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ANNALS OF
INTERNAL MEDICINE

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COLLAPSE THERAPY OF BRONCHIECTASIS *

By E. RIST, M.D., *Paris, France*

IT was to be expected that artificial pneumothorax, having proved so strikingly efficient in healing ulcerative tuberculosis of the lungs, should also be attempted as a therapeutic measure against bronchiectasis. Indeed the attempt was made for the first time as early as 1903 by one of Forlanini's most brilliant followers, Riva-Rocci; and it was, we hear, crowned with success. Since then several authors have published cases of bronchiectasis treated by pneumothorax, with a variety of results; but the sum of those cases amounts to a comparatively small total. Whittemore and Balboni could in 1928 gather only 93 of them out of the world literature. It seems, therefore, as if each series consisted of only a few cases, none of the authors having been persevering enough to give the method a systematic trial. As a matter of fact, this method of therapy has not become widespread, and one still meets with skepticism or reluctance on the part of the practitioner, when proposing to collapse by pneumothorax a lung affected with bronchiectasis. Yet there has been lately the reverse from indifference regarding the disease itself, to wit the remarkable improvements which radiography after injecting the bronchial tree with iodized oil, to say nothing of bronchoscopy, have achieved in its diagnosis.

I think some misconceptions have been at work to prevent physicians from taking advantage as often as they should of the resources which artificial pneumothorax puts at their disposal against bronchiectasis. In the first place, they are not sufficiently aware that there is no such thing as spontaneous recovery from that malady. One still reads in some textbooks and articles that recovery may occur and consequently justify expectancy. But, to my knowledge, no valid instance has ever been produced. In the second place one is too apt to forget that it is not only an incurable, but, in the long run, a deadly disease. It is true that it may for some time—months or even years—remain a comparatively harmless ailment, as long as the suppuration is due to the ordinary aerobic micrococci. Sooner or later, however, a time inevitably comes when the bronchiectatic focus is invaded by

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anaerobic bacteria and eventually by the spirochetes, which give the infection its peculiarly serious septic character. The change is signalized by the offensive nature of the discharge, which was previously odorless.

Once this stage has been reached, the patient, although his general condition may at first remain tolerably good, is threatened by all the dangers which attend anaerobic infection of the lung. Multiple small abscesses develop in the neighborhood of the cylindrical bronchiectases and add to the lipiodol roentgen-ray picture the characteristic pigeon-hole or grape-bunch features. Various circumstances favor acute revivals of the infectious process, which may extend to further parts of the lung, either in the immediate vicinity of the primary focus, or by way of embolism, to more distant parts of the same or to the opposite lung. Real gangrene of the lung is liable to occur in such circumstances. If the process extends to the visceral pleura and there are no adhesions, a putrid, offensive empyema is not seldom observed. Sometimes a more or less evident pyemia occurs with septic emboli which have a curious propensity to localize either in the medulla of the long bones or in the substance of the brain. The metastatic abscesses thus produced are always characterized by their foul, offensive odor. I should mention also the very profuse recurrent hemorrhages which complicate some cases.

Even if the patient does not succumb to one or several of the aforenamed accidents, he is sure to reach a period when progressive wasting, cachexia and eventually amyloid will put an end to his life. It matters little whether the whole story runs along for three or 10 or 25 years. Bronchiectasis is a disease which finally kills, be the end as protracted as we may pray for. Therefore, if one keeps this in mind, one must feel that it should be treated as early and as effectively as possible.

There is another misconception which has prevented many a physician from attempting pneumothorax, namely the notion that bronchiectasis is almost always accompanied by symphyseal pleural adhesions rendering a trial perfectly useless. Now I think it is always unwise to predict confidently the presence (or the absence) of adhesions, even when the history of the patient and his physical and roentgen-ray examination seem to overwhelm us with evidence, because the only definite evidence is the failure of our attempts to create a pneumothorax. As a matter of fact, there is very little truth in the widespread notion that adhesions are almost the rule in bronchiectasis. Among the 93 cases collected from the literature by Whittemore and Balboni, 12 only had adhesions which made a collapse impossible. Of course, the 93 cases being, as I have said before, the sum of numerous isolated cases or small series of cases published by a number of authors, one may presume that many a failure caused by adhesions has escaped publication. The percentage of 12.9 resulting from these figures is evidently much too low. In the rather large series of personal cases which I shall presently discuss, I find 37.2 per cent of failures attributable to adhesions, a little more than one-third. Tabulating in 1926 more than a thousand per-

sonal cases of tuberculosis treated by pneumothorax, I found the number of failures due to extensive adhesions to be one-fourth of the total. Even admitting, therefore, that adhesions are somewhat more frequent in bronchiectasis than in tuberculosis, still certainly the difference is not such as would justify abstention by principle from pneumothorax in bronchiectasis, while there is now a consensus of opinion that pneumothorax is, or ought to be, the routine treatment of ulcerative tuberculosis.

Furthermore, I feel certain that the proportion of pleural adhesions is greater in cases of long standing than in recent cases. There is therefore good reason to believe that if we treated bronchiectasis earlier and more systematically with pneumothorax the proportion of failures caused by adhesions would be less. And finally if we fail to collapse the lung by pneumothorax, we may try to collapse it by phrenicectomy.

I now wish to present a short account of the cases of bronchiectasis which have been observed in my Hospital-Department during a period running from 1920 up to the end of 1931. Their total number is 90, of which 31 were not submitted to artificial pneumothorax, either because they refused treatment and were ultimately lost sight of, or because they were admitted in an extremely serious condition, precluding any sort of active therapeutic measure. As a matter of fact, the five patients belonging to this last group died in the wards soon after admission, one with abscess of the lung, two with lung gangrene, and two with septic bronchopneumonia.

In 59 cases, artificial pneumothorax was attempted. We failed to create it in 22 cases, the pleura being totally or extensively adherent. Among the 37 patients whose lung could be successfully collapsed 17 were not benefited by it. Six of these 17 had adhesions of the diaphragmatic pleura; therefore, although the rest of the lung was well collapsed, its inferior part, where the lesions were located, remained uninfluenced. In one other patient the lung was beautifully collapsed; in fact he was one of the most remarkable instances of perfect collapse which I have ever witnessed: the lung was reduced to the size of a fist around the hilus. But we soon noticed that each refill of the pleural cavity with air stopped the discharge entirely and was followed by high fever. If we let the lung expand again to a certain degree, an abundant foul discharge of pus began to flow and the fever subsided. The roentgen-ray picture showed, in the center of the collapsed lung, a small, walnut-sized, round cavity half filled with fluid. Evidently the collapse produced a kink of the evacuating bronchus and consequently a retention of the purulent discharge. We tried in vain to approximate a medium pressure which would facilitate drainage and exclude retention, and the treatment had to be abandoned. The remaining 10 unsuccessful pneumothorax cases were either cases of bilateral bronchiectasis or were complicated with gangrene of the lung and ultimately died.

There remains a group of 20 patients, one-third of the total, who derived the greatest possible benefit from pneumothorax treatment. They were rapidly made free of all morbid symptoms; their discharge rapidly disap-

peared, they ceased coughing, running fever and losing weight; they were to all appearances restored to health. It is true that for seven of them the recovery was conditional to the maintenance of lung collapse. If we allowed the lung to expand, the symptoms, after a certain time, would appear again, to vanish once more as soon as the pleural cavity was refilled with air. Even such a conditional recovery is of considerable benefit. After all the slavery of refills (if it may be so-called) compares most favorably with the awful slavery of the foul stinking spittoon. Not only did the collapse treatment in those imperfect cases protect the patients against the dangerous complications referred to previously, but it enabled them to lead a normal life, to sustain themselves by their daily work and to be relieved from the social ban caused by a disease which made them repulsive and undesirable. One must not forget that the unfortunate bearer of a bronchiectasis is not seldom made an outcast by his fellow-workers. One of my patients, whose lung could not be collapsed on account of adhesions, finally committed suicide for precisely that reason.

In 13 cases the success of pneumothorax was unconditional, complete, permanent and has lasted up to the present time for three, five, six and eight years after the treatment was stopped. My earliest case, which does not appear in these hospital figures, and whose pneumothorax was induced in January 1914 and abandoned in August of the same year, has now been free of symptoms for nearly 19 years. Not the least interesting feature of these recoveries is the rapid return to a normal shape of the pronouncedly drumstick shaped fingers, which are so characteristic of bronchiectasis.

It is often claimed that the scope of pneumothorax treatment is limited to bronchiectasis of short duration, especially in children. This may be true in a general way. I wish nevertheless to emphasize the fact that, among my recoveries, figures the case of a boy of nine whose treatment was initiated after he had been ill for seven years, and that of a girl of 20 who had been ill for more than 10 years. Another case concerned a gentleman aged 59, who had been ill for two years. There are therefore exceptions to that assumed rule. Anyhow this should be an inducement to have recourse to pneumothorax treatment as early as possible.

I feel pretty certain that if bronchiectasis were always diagnosed early—as it indeed should be nowadays since the use of iodized oil has proved an infallible method of demonstrating the presence of dilated bronchi—and if the pneumothorax treatment were always initiated as soon as the diagnosis had been established, the proportion of recoveries would increase very substantially. Many years were lost before the necessity of early pneumothorax treatment in ulcerative tuberculosis of the lung was universally admitted. But since it has been admitted, the proportion of successes has become considerably greater than it was in the days when pneumothorax was regarded as an exceptional measure and, so to say, as a last resource. I venture to predict that the pneumothorax treatment of bronchiectasis will be a repetition of the same story.

But there are failures, and there always will be failures, the most usual cause of which is the early formation of symphyseal adhesions. In this conjunction again the lesson which collapse therapy of lung tuberculosis has taught us should not be lost. In other words we should, without loss of time, take advantage of the second best and least harmful form of collapse therapy, namely avulsion of the phrenic nerve. In 11 of my cases of bronchiectasis in which adhesions had caused the failure of pneumothorax, phrenicectomy was performed: three patients made a perfect, complete, permanent recovery; four other patients were greatly improved but not cured. What the proportion may be of patients who, having derived benefit neither from pneumothorax nor from phrenic avulsion, can be notably improved or definitely cured by lobectomy, it is almost impossible to say at the present time. But I shall certainly raise no difference of opinion in this assembly if I confidently assume that whatever the successes of surgery in the treatment of bronchiectasis may be in the future, they will always be associated with the name of Professor Archibald, of the city of Montreal.

Now, it will be asked, how is the healing of the bronchiectatic condition by lung collapse to be interpreted? One who has seen, at autopsy, those bronchial cavities, flattened and distorted as they are, with their thickened, inelastic walls embedded in thickened inflammatory lung tissue, can hardly imagine that collapse could bring back the dilated bronchi to their normal state. It is true that only those cases come to autopsy which have lasted a comparatively great length of time. If we could study the lesions in the earlier phases of the disease, we would probably find them more likely to be favorably influenced by collapse. Nevertheless it sometimes happens that when iodized oil is injected into the bronchial tree of a former patient who has recovered after pneumothorax treatment or phrenic avulsion, the roentgen-ray picture shows evidence of persistent bronchial dilatations. The question therefore arises of what has been really achieved by collapse. I think it is not very difficult to answer that question. Collapse has made an efficient and thorough drainage of the bronchial tree possible and consequently paved the way for a gradual, spontaneous healing of the bronchial, or to be more precise, of the bronchopneumonic infection. I conceive that all the symptoms of bronchiectasis are due to infection and not to dilatation. A non-infected bronchiectasis is an anatomical abnormality. It is not a disease.

BILATERAL SPLANCHNIC NERVE SECTION IN A JUVENILE DIABETIC*

By GEZA DE TAKATS, M.D., and G. K. FENN, M.D., *Chicago, Illinois*

ONE of us, with Cuthbert,[1] reported that excision of the celiac ganglion in the dog resulted in a decided and persistent rise in sugar tolerance. Further analysis of the mechanism of the increase in tolerance showed that bilateral adrenal denervation or bilateral splanchnic section gave identical results.[2] It was suggested in the first paper that the exclusion of sympathetic nerve impulses may bring about either an increased insulin production or a reduction in the insulin requirement. The susceptibility of the dogs to insulin was markedly increased after either of these operations, a fact previously observed by several workers.[3]

Such a state of diminished insulin requirement and increased insulin susceptibility would be highly desirable in diabetic patients. In previous attempts to increase sugar tolerance in diabetes [4, 5, 6] it was pointed out that in the severe type of juvenile diabetes, with frequent occurrence of acidosis and coma at the slightest infection or trauma, an operation would be justifiable if nothing but a stabilization of tolerance could be accomplished. Such an object was sought by producing islet-hypertrophy in the ligated tail of the pancreas, which resulted in a decided rise of tolerance in one, and an indefinite temporary rise in a second diabetic child. It was pointed out, however, in previous publications [4, 5, 6] that such an operation did not strike at the real cause of diabetes, because unless one would be able to protect the new islets from injurious effects of nervous or hormonal origin, the new islets would become exhausted like the original ones.

Resection of splanchnic nerves, while a much used experimental procedure, has been performed but a few times in man. Thus far, most of the studies in regard to technic have been carried out on the cadaver, and transpleural,[7] supradiaphragmatic,[8] infra-mediastinal,[9] and suprarenal [10] approaches have been suggested. A critical summary of splanchnic section for relieving upper abdominal pain has been presented by Alvarez.[11] All these operations have been performed either with the object of relieving painful crises (Jean,[7] Foerster,[12] Mixter and White [13]) or to relieve gastric atony (Pieri [8]). The latter has performed unilateral splanchnic resection seven times to increase gastric tone and peristalsis. To our knowledge, splanchnic resection for diabetes has not been performed before.

The depression of sympathico-adrenal function by adrenal denervation, however, has been suggested by Crile in cases of neurocirculatory asthenia, recurrent hyperthyroidism and peptic ulcer.[14] In a personal communication,

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Dr. Crile stated that he had also performed this operation for diabetes but could not make any statements as to the results. The Italian surgeons Donati [15] and Ciminata [16] suggested adrenal denervation in diabetes. Donati denervated the left adrenal in a fifty year old marantic diabetic woman, whose blood sugar fell but later returned to a slightly lower than preoperative level. She needed less insulin than before.

Our reason for selecting splanchnic section instead of adrenal denervation to depress sympathico-adrenal function is as follows: The splanchnic nerves control a far larger area than the suprarenal fibers; an increased blood supply to the pancreas may be of benefit. Secondly, the excision of a long segment of both splanchnic nerves may insure lack of regeneration better than section of nerve fibers going to the adrenals. Crile [14] doubts the possibility of regeneration in adrenal nerves, but our animal experiments uniformly indicate a great regenerative power of the splanchnics. It must be admitted that splanchnic section alone does not denervate the adrenals completely, because of the fibers coming to adrenals from the celiac ganglion and the upper lumbar ganglionated trunk. Nevertheless, in our animal experiments,[1, 2] celiac ganglionectomy, complete adrenal denervation and bilateral splanchnic section gave identical rises in tolerance. For this reason splanchnic resection was selected in the case to be described.

Investigation of the various methods of approach revealed the supradiaphragmatic, retropleural approach as the most desirable for our purpose. Aside from the advantage of avoiding an intraperitoneal or retroperitoneal operation with the subsequent difficulty of postoperative feeding, the nerves can be exposed at great length above the diaphragm and an excision of two to three centimeters is possible. Observations on the dog indicated that astonishing distances of splanchnic defects can be bridged by regeneration.

In the selection of a suitable patient for such an operation we were guided by the principles discussed in a previous communication [6]: namely, the severe type of juvenile diabetic, with unstable tolerance, and one that has been diabetic for at least two years and controlled for several months previous to operation. As stated by Allen and Wilder,[17] juvenile diabetes starts with unusual severity and with adequate dietary and insulin control the tolerance may gradually improve. The absence of vascular damage, which may occur so early in juvenile diabetes,[16] can be checked by ophthalmoscopy and films of peripheral vessels. Tests to demonstrate the effect of sympathetic depression on the carbohydrate metabolism of the selected patient will be discussed under the comments.

Case History

D. H., an 18 year old colored girl, was admitted on October 17, 1932, to St. Luke's Hospital. Her great grandmother died of diabetes. She had had whooping cough, chicken-pox and measles. At the age of 12 and again at the age of 15 she had an acute attack of abdominal cramps, became very thin and lost weight. This could hardly have been due to diabetic acidosis as she promptly recovered from both attacks and was quite well until January 1932 when polydipsia and polyuria set in.

She lost 50 pounds in three months, became very nervous, "jumpy." The patient stated that she never liked or ate sweet foods, as they caused abdominal cramps. At the end of March 1932, because of frequent colds, a tonsillectomy was done, following which she became drowsy. It was at this time that her diabetes was first discovered. The CO_2 combining power went down to 26, the blood sugar rose to 430 milligrams per 100 c.c. She was admitted under the care of one of us (G. K. F.). Two hundred and thirty-five units of insulin were given during the first 15 hours, together with glucose, fluids and caffein. She was finally discharged on a diet of C 100, P 60, F 175, with a glucose value of 151, representing 2311 calories; 35 units of insulin to be given in the morning and 25 units in the evening. The glucose-insulin ratio was 2.5 : 1.

During the interval between her discharge from the hospital and readmissior the patient was infrequently observed in the out-patient department. Because c circumstances beyond control, her regulation, even on this dose of insulin, was insufficient.

She was a fairly well nourished colored girl, rather nervous, but alert. Except for a small colloid goiter without accompanying signs of toxicity, no abnormalities were seen, palpated or heard. A right lower molar tooth was found to be infected and later extracted. While she had had dietary instructions and took her insulin regularly, there was an intermittent spilling of sugar. There was no evidence of peripheral vascular change due to diabetes. Both diaphragms moved well and the phrenico-costal angles were clear, a point we wished to be sure about, because of the planned supradiaphragmatic approach to the splanchnic nerves. The preoperative diet was C 75, P 50, F 150, a glucose value of 120 covered with 40 units of insulin. She was, however, not entirely regulated on this regime, and was very unstable.

Preoperative studies revealed that ergot definitely depressed the galactose tolerance curve (figure 1). This we took as being suggestive of a sympathetic hyper-

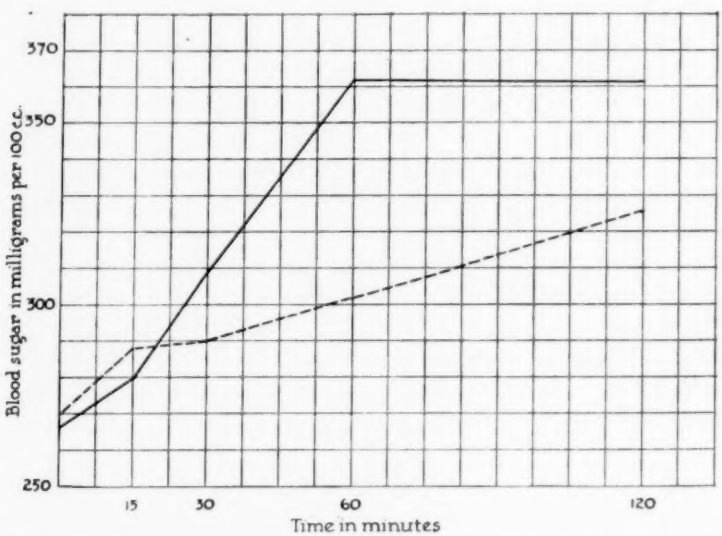

FIG. 1. Galactose hyperglycemia curve. Forty grams of galactose were given in 500 cubic centimeters of water. Blood sugars were determined by the modified Folin-Wu method, before, 15, 30, 60 and 120 minutes after the administration of galactose. Straight line: galactose without ergotamine. Interrupted line: galactose with 0.5 mg. of ergotamine under the skin. Note the marked depression of hyperglycemia at one hour.

irritability of the glyco-secretory mechanism. An insulin sensitivity test was run, with the idea of comparing it with others after the operation (figure 2).

After the customary preoperative preparation as required in diabetes [6] section of the left splanchnic nerves and thoracic chain was done on October 22, 1932. Under ethylene-novocaine anesthesia a left paravertebral incision was made, exposing the eleventh and twelfth ribs and transverse processes. The vertebral ends of the two ribs were resected for a distance of an inch and the transverse processes were bitten off with a double-action bone forceps. The endothoracic fascia was incised and the pleura was peeled away from the lateral surface of the vertebral column, just above the diaphragm. A slight tear occurred in the pleura during this procedure,

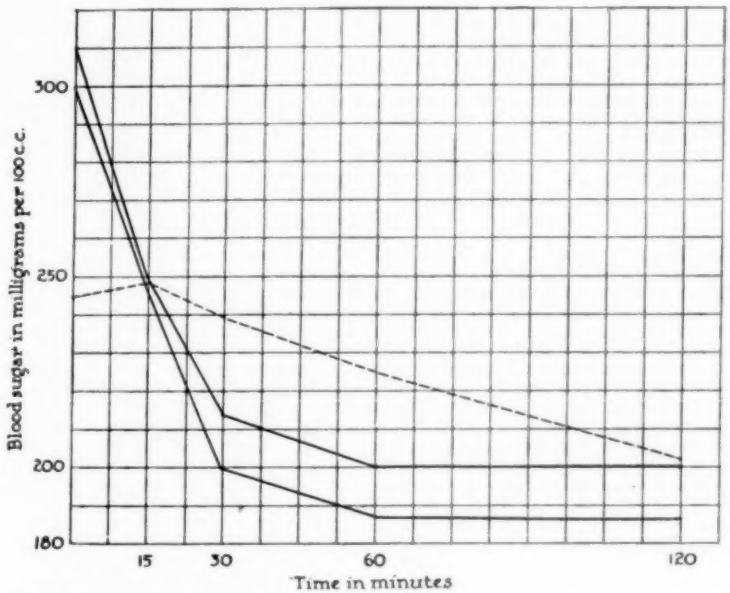

FIG. 2. Insulin sensitivity test. One-tenth of a unit of insulin per kilogram body weight was given intravenously and blood sugars were determined by the micro-Folin-Wu method at intervals. Interrupted line: preoperative curve. Straight lines: postoperative curves taken a month apart. Note the delayed response to insulin before the operation. Following the operation, the blood sugar drops rapidly at 15 and 30 minutes and there is no rise between the first and second hour as if epinephrine response would be inhibited. Urinary sugars taken simultaneously with the blood sugar determinations revealed the renal threshold around 200 milligrams of dextrose in 100 cubic centimeters of blood.

but it was quickly repaired with a fine catgut suture. The left splanchnic nerves and the thoracic sympathetic trunk were picked up with a nerve hook and were sectioned. The long muscles of the back and the lumbodorsal fascia were sutured with interrupted No. I chromic catgut sutures. The skin was closed with interrupted silk sutures.

The pulse and general condition of the patient were good at the end of the operation. The pulse was 116 at the start (excitement) and 112 at the end of the operation. There was a slight pneumothorax in the left chest cavity. For the first two days 2,000 c.c. of 5 per cent dextrose and 1,000 c.c. of normal salt solution were given under the skin daily. Insulin was given in doses regulated according to the urinary tests, which were made every four hours. She received from 40 to 45 units of insulin a day. On the third day a soft and on the fifth day a more solid diet was

given, containing 120 grams of available glucose. Severe cramping in the epigastrium was controlled by atropine (gr. 1/150) twice a day. The possibility that this represented an exacerbation of an old pancreatitis was considered but ruled out by the low figures for blood-diastase, using a method described elsewhere.[17]

The patient made a rapid convalescence. The wound healed by primary intention. With the same diet as before the operation, there was a reduction of the insulin requirement to one-half of the preoperative amount. On November 12, 1932, three weeks after the first operation, the right splanchnic nerves were exposed. The approach was similar, except that the paravertebral incision was continued along the twelfth rib laterally for 6 to 8 centimeters and both skin and musculature were transected. This addition to the original incision facilitated exposure considerably. The vertebral ends of the eleventh and twelfth ribs and the transverse processes were removed. The peeling of the pleura did not result in any tear on this side. The identification of the structures was not as clear, but three definite white strands were cut and removed for a length of three centimeters. Histologic examination revealed one definite nerve trunk. Because of the uncertainty of complete transection, one cubic centimeter of 95 per cent alcohol was deposited in the posterior mediastinum paravertebrally. The wound was closed in layers.

The postoperative convalescence was uneventful. The patient was put on the same diet again with 120 grams of available glucose, and required from 20 to 25 units of insulin. An attempt to discontinue all insulin for a week resulted in the spilling of 49.47, 28.9, 48.15, 63, 75, 71.7, 30, 42.75, and 76.59 grams of glucose on eight successive days. As the patient was nearing coma, insulin was again given and the diet was increased to promote regain of weight. She was discharged on December 19, 1932, on the original preoperative diet of P 50, C 75, F 150, A.G. 120 and 20 units of insulin. She was seen at intervals and two more insulin sensitivity tests were obtained. Her weight was 114 pounds before operation and had gradually risen to 127 pounds on February 25, 1933. There was no pain or inhibition of motion in the back. (Figure 3.)

In addition to studies on insulin sensitivity, blood pressure measurements were taken to see whether splanchnic section might have any depressing effect on blood pressure. No preoperative reading is available. One week after the second operation the blood pressure was 90/68 lying flat in bed. After standing three minutes, blood pressure was 82/62. Five weeks after the operation, blood pressure was:

96/80	lying down
86/70	standing five minutes
100/80	after hopping ten times.

Fifteen weeks after the second operation, the patient's blood pressure was:

110/80	lying down
108/80	standing five minutes
115/80	after hopping ten times.

This temporary fall in blood pressure, which is regained after fifteen weeks, closely resembles the experimental findings of Bradford Cannon,[20] who found in cats that a progressive removal of the sympathetic ganglionated cord and splanchnic nerves is followed by a fall in blood pressure and then a return to normal. Even completely sympathectomized cats maintained a normal blood pressure.

Comment

The operation here described resulted in an abrupt change of the glucose: insulin ratio of the diabetic child from 2.5 : 1 to 5 : 1. This change occurred after section of the left splanchnic nerves, whereas the later sectioning of

the right splanchnic nerves did not produce any further improvement. During the postoperative period of four months the patient not only regained her original preoperative weight (114 pounds), but increased it to 129 pounds. It is of some significance that several subsequent attacks of upper respiratory infection did not upset her insulin requirement. This now seems

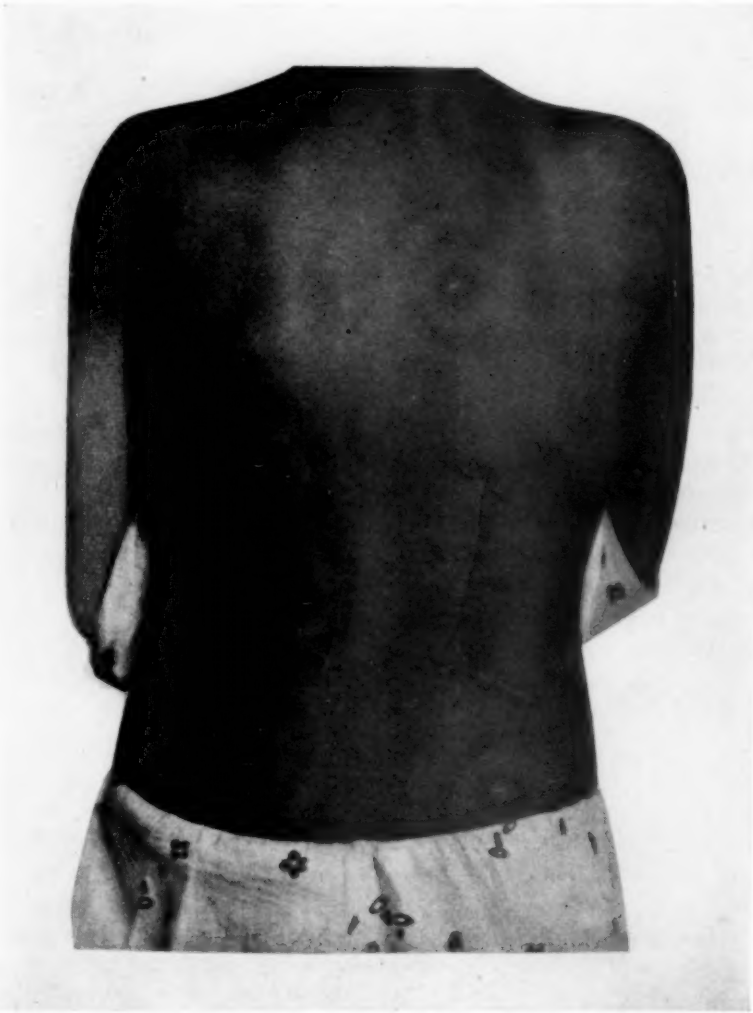

FIG. 3. Photograph of patient's back two weeks after second operation. Both incisions healed by primary union. The muscles of the back show no atrophy and there is no limitation of motion and no neuralgia. Note the rectangular incision on the right side, which facilitated exposure.

to be stabilized at 20 to 25 units for a diet of 120 grams of available glucose. We are, of course, aware of the spontaneous fluctuations of tolerance in diabetic patients, and particularly of the improvement of tolerance in hospital-

ized patients, who can be far more closely controlled than the ambulatory ones. In this instance, however, the patient was not controlled after the operation, but on the contrary all insulin was withdrawn for a whole week to see how much the patient's own insulin output had improved. And yet a very definite improvement of the glucose: insulin ratio resulted. The improvement occurred immediately after section of the left splanchnic nerves and did not increase after the section of the right splanchnic nerves. Whether this indicates a predominating influence of the left splanchnic nerves on bilateral adrenal secretion or whether the nerves had not been all severed on the right side cannot be decided at present.

One might assume that there was no increased insulin secretion in this child following the operation, because large quantities of sugar were excreted on the preoperative diet when insulin was discontinued. But the insulin sensitivity of the patient had increased. (Figure 2.) It will be noted that the preoperative administration of 0.1 of a unit of insulin per kilogram body weight given intravenously produced no drop of blood sugar at 15 and 30 minutes, and even after an hour it had only dropped from 245 milligrams to 225 milligrams, a slight drop of 8 per cent. After the operation, however, the two tolerance curves, which check remarkably well with each other, show a marked drop at 15 and 30 minutes. The average drop at one hour from 305 to 193 milligrams represents a 36.7 per cent drop, and this level is maintained for another hour.

The test for insulin susceptibility can readily separate insulin-resistant patients from those that are insulin sensitive. It is possible that different types of diabetic patients will be thus distinguished from each other, although much experimental and clinical work is yet to be done to establish the value of insulin sensitivity.[1]

We have also tried to elicit some objective sign of sympathetic hyperirritability in this patient and, following the suggestion of Pollak,[21] have administered 40 grams of galactose to the patient, followed by blood sugar determinations. According to this author, 0.5 milligram of ergotamine inhibits the galactose hyperglycemia in one group of diabetics, and it is this type of diabetic we are interested in, in whom the sympathetic depressor action of ergot imitates the surgical effect of splanchnic section. This patient showed a definite inhibition of the galactose hyperglycemia, following the subcutaneous administration of ergot. (Figure 1.) At present we are engaged in other tests which would imitate the effect of a bilateral splanchnic section on a blood sugar curve.

What the discovery of insulin has meant to the diabetic, but particularly to the diabetic child, has been repeatedly emphasized.[15, 16] Juvenile diabetes before the insulin era was almost always fatal. Unfortunately, however, the low mortality statistics of Joslin, Wilder and Allen, and Priscilla White cannot be reproduced in the country at large. Wilder [22] has recently stated that the death rate from diabetes is actually mounting and that diabetic patients throughout the country are either not using insulin or not using it

properly. In Ontario, where insulin is provided free of charge to charity patients, none had been used in 44 per cent of 192 cases of fatal diabetes and in only 12 per cent had it been used with any regularity.[21] In Oregon, only one of two patients who died of diabetes used insulin at any time, only one in four used it in the final illness, and only one out of three knew how to test for sugar in the urine. In this state only 15 per cent of the fatal cases had ever used insulin regularly,[22] and in the state of Washington, only 16.5 per cent used it.[23] The actuarial statistics of the Metropolitan Life Insurance Company portray a very sad picture of diabetic mortality (cit. by Wilder [22]). The physical surroundings and the economic difficulties of certain types of diabetic children are such that an adequate dietary and insulin control is not feasible. Thus in addition to other considerations, a definite social and economic indication must be recognized in the selection of diabetic children for operation.

The present report is considered as a preliminary step toward a thorough investigation of various types of juvenile diabetic patients. A patient with a severe type of uncomplicated juvenile diabetes, who was poorly controlled but had not yet developed detectable vascular damage and in whom a supression of sympathetic glyco-secretory discharge could be accomplished with ergot, has proved to show stabilization and improvement following splanchnic nerve section.* Her insulin resistance has been modified. Only a careful selection of future cases, with observations over a prolonged period of time, will establish the value of this operation.

Summary

Bilateral splanchnic section was performed on an 18 year old diabetic girl with the purpose of stabilizing and increasing her sugar tolerance. There has been an immediate drop to one-half of her previous insulin requirement, which seems to be due to an increase in insulin sensitivity and which has persisted up to the present writing, four months after the operation. Further studies with a final report will be made at a later date.

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* Nine months after operation the daily insulin requirement is still 20 units. The fasting blood sugars are between 120 and 146 mg. per 100 c.c. Without our knowledge the patient married in the meantime and is now in the fourth month of pregnancy. The effect of pregnancy on her tolerance will be followed and reported later. At present, her diabetes is stable, mild, easily controlled. A second diabetic child, recently operated upon, made a smooth postoperative convalescence.

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CHRONIC ARTERIAL OCCLUSION OF THE EXTREMITIES *

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CLINICIANS have long recognized that certain conditions, usually of a chronic nature, which affect the extremities and commonly terminate in gangrene, result from insufficient circulation. With the demonstration by Raynaud that gangrene could develop without vascular occlusion, these conditions were divided into two groups: (1) those due to structural disease of the arteries, described and classified under the general term arteriosclerosis; (2) those due to functional disturbance of the arteries without structural change: for example, Raynaud's disease. The accepted neurogenic origin of the vascular disturbance in Raynaud's disease and in the condition described later by Weir Mitchell as erythromelalgia and the similarity of many of their symptoms to those found in certain purely nervous conditions have caused them to be described and classified among diseases of the nervous system under the heading of vasomotor and trophic neuroses. As a result, both these conditions have attracted the attention of the neurologist rather than of the clinician interested in cardiovascular disease. The demonstration by Buerger [1] of the nature of one form of structural vascular disturbance, namely, thromboangiitis obliterans, and his later publication of a textbook on "Circulatory Disturbances of the Extremities" [2] have been distinct contributions to our knowledge of vascular affections of the extremities. Buerger was one of the first to apply in a systematic manner the new knowledge concerning the physiology of the capillary system to the study of peripheral vascular disturbances, and to stress its value in diagnosis. With the limited exact knowledge available up to that time of the normal function and control of the capillary system, it is not surprising that in clinical textbooks little or no mention was made of the rôle of the capillaries in circulatory disturbances. Thanks to the studies on the anatomy and physiology of the capillaries, particularly to those of Krogh [3] and his pupils, and to the work of Lewis [4] and his associates on the response of the blood vessels of the human skin, it has become possible for clinicians to interpret more intelligently the abnormal changes occurring in the skin following disturbances in the circulation, and to appreciate more fully their significance in the diagnosis and treatment of vascular affections.

It would appear fortunate that, at this stage in the development of our knowledge the operation of ganglionic sympathectomy was introduced by the surgeon as a means of treatment for increasing the blood flow to extremities affected by vascular disease. Being a therapeutic measure, it

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stimulated a wider interest among clinicians, both physicians and surgeons, in peripheral vascular disturbances. A number of workers, notably Lewis,[5] Brown and Adson,[6] White,[7] Scott and Morton,[8] to mention only a few, have made carefully controlled observations before and after sympathectomy on patients suffering from different types of vascular disturbance. These investigations have given us a better and clearer understanding of the nature and origin of circulatory disturbances occurring in the extremities.

When one reviews the present situation, it is observed that no new type of vascular disease has been found since Buerger gave us a pathological and clinical description of thromboangiitis obliterans, and that no change has been made in the classification of peripheral vascular disease into two main groups: one, organic or obliterative; the other, functional or vasomotor. The clinical manifestations, however, have become fairly well defined and one has a much clearer conception of the causal relationship of functional disturbances in different parts of the vascular system to the production of the symptoms and signs present in various types of peripheral vascular disease. With our present knowledge and methods for the examination of the circulatory efficiency of the extremities, the different types of vascular disease can be accurately diagnosed and, in the majority of cases, this can be accomplished by the regular bedside or office methods of examination. As yet, proficiency in accurate diagnosis is confined largely to those especially interested in local vascular disturbances. Failure to make a correct diagnosis is common and is due chiefly to a lack of appreciation of the diagnostic significance of the local signs and symptoms associated with disturbances of function of the peripheral vascular system from the small arteries to the venules. There may also be failure to recognize that functional vascular disturbances are often prominent in the obliterative type of vascular disease. Much confusion in diagnosis would disappear if physicians generally took a keener interest in the significance of these disturbances and if writers of textbooks of medicine would direct the attention of the reader to the vascular origin of Raynaud's disease, erythromelalgia, and allied vascular disturbances by discussing them under vascular disease rather than under vasomotor and trophic neuroses of the nervous system. In a recent textbook of medicine, this change in the usual classification has been adopted.[9]

In suggesting that Raynaud's disease and erythromelalgia be classified as vascular disease rather than disease of the nervous system, I am not unmindful of the fact that many of the local subjective symptoms and many of the changes occurring in the skin and subcutaneous tissue, found in these conditions, are present in certain primary diseases of the nervous system, and may be considered adequate justification for their classification under this system. However, it is becoming more and more evident that trophic disturbances, and probably many of the peripheral symptoms found in primary affections of the nervous system, are of vascular rather than of nervous origin. The fact that cases of Raynaud's disease, with or without scleroderma, experience relief of symptoms and show improvement of the trophic

changes in the skin and subcutaneous tissue following sympathectomy indicates that interference with the normal blood flow plays an important, if not the essential, rôle in their production. In support of this view is the favorable influence of increased blood flow following sympathectomy on trophic changes and possibly on the growth of the limb in poliomyelitis (Harris [10]), and on the healing of perforating ulcer in degenerative lesions of the nervous system (Fraser [11]). Further, it would appear that sclerotic vascular changes are responsible not only for the well known obliterative vascular disturbances in diabetes mellitus, but are the primary cause of the symptoms of peripheral neuritis, if present (Woltman and Wilder [12]). Is this not adequate justification for a more conscious recognition by clinicians generally of the vascular origin of nutritional disturbances and of many symptoms occurring in the extremities in certain diseases primarily affecting the nervous system?

As to the nature of the lesions in different types of peripheral vascular disease, structural changes of the arteries in the obliterative group and vasospasm or vasodilatation in the functional group are the immediate causes of the circulatory disturbances. The common clinical conditions belonging to the obliterative group are thromboangiitis obliterans and peripheral arteriosclerosis of advancing years or occurring with diabetes mellitus. The vascular changes in thromboangiitis obliterans, as demonstrated by Buerger, have a definite character quite distinct from those found in peripheral arteriosclerosis. The early lesion is an inflammation of the wall of the larger arteries, chiefly of the lower extremity, beginning in the adventitia and involving all coats of the vessel, finally causing thrombosis followed by organization and canalization. The lesions are multiple, affecting different segments of the vessels, and in the examination of an amputated limb different lesions are found to show varying stages of acute and chronic inflammation. While the veins may be involved in a similar process, disease of the arteries with occlusion is the chief and primary cause of the circulatory disturbances.

Unless sudden occlusion of a vessel occurs, circulatory disturbances may be absent in the early course of the disease. If the part affected is subjected to exercise, the first complaint is fatigue and aching upon exertion; later, the pain of intermittent claudication develops, which we now know to be due, not to spasm of the artery, but to chemical changes occurring in the muscle resulting from a deficient blood supply. Vasospastic or functional disturbances may occur at this stage: numbness, tingling, and sensitivity to cold causing pallor or cyanosis. In some cases these symptoms may be more or less prominent and lead to the erroneous diagnosis of Raynaud's disease. Coldness is present and, in the dependent position, rubor of the distal parts develops, and pallor in the elevated position. The capillaries are dilated and partially paralyzed.

With the diminution of the blood supply to the minute vessels of the skin, nutritional or trophic changes in the skin and nails develop. As is

found in peripheral arteriosclerosis, external trauma plays an important rôle in accelerating the development of these changes and finally causes ulceration and gangrene. After nutritional changes make their appearance, the most distressing symptom for the patient is the pain which occurs in the distal parts of the extremity during rest. It may occur without the appearance of ulceration or gangrene. Metabolic changes in the tissues, resulting from deficient circulation, rather than involvement of the nerves in the perivascular inflammation at the site of the lesion, would appear to be the chief cause of rest pain. Edema may occur due to occlusion of the veins or from posture in the later stages of the disease. In thromboangiitis obliterans the important clinical manifestations are: pain of intermittent claudication; postural color changes; coldness; peripheral nutritional changes in the skin and nails; rest pain; and absence of pulsation in palpable arteries distal to the arterial occlusion. These symptoms develop as a result of occlusion of a large artery, or arteries, of the extremity.

In the arteriosclerotic type of vascular disturbance, occlusion of one or more arteries of the size commonly affected in thromboangiitis obliterans has been given as the chief cause of the disturbances resulting from the defective peripheral circulation. When one compares the character and distribution of the arteriosclerotic lesions in the peripheral arteries with those found in thromboangiitis obliterans not complicated by arteriosclerosis,—the poor collateral circulation in arteriosclerosis and the relatively good one in thromboangiitis obliterans following occlusion—it is difficult to accept occlusion of a large artery as the chief cause of the clinical manifestations in peripheral arteriosclerotic disease.

In the larger arteries of the leg, the primary lesion in arteriosclerosis is a medial degeneration with later calcification producing the beaded type of artery often found on palpation of the radial. The arteries usually affected are the femoral, popliteal, peroneal and radial; less often, the tibial and brachial; and very rarely, the dorsalis pedis. This degeneration of the media impairs the elasticity of the vessel and its lumen becomes larger than normal (Klotz [13]). Intimal thickening may develop as a secondary process but does not cause any significant occlusion unless thrombosis occurs. However, in the branches of these arteries supplying the muscles, bone and skin, intimal thickening without significant medial change develops as a primary process and produces partial occlusion of the main small branches and partial or complete obliteration of their more distal portions. Just as thickening of the intima in the renal artery and its main branches may narrow the lumen and lead to nutritional changes in the kidney, atrophy of muscles and skin may follow similar changes in the smaller arteries of the limb.

In this connection, I recall very vividly an incident which happened during my last visit to the late Sir James Mackenzie. He picked up the thin skin on the back of his hand, and said: "What causes that?" Let me quote from his textbook on angina pectoris: "If we wish to grasp the meaning of the nature and significance of a great many symptoms of dis-

ease, we should look at the changes that occur in the progress of the healthy man from the cradle to the grave." Again: "A great many symptoms of disease owe their production to the impaired function of organs brought about by the diminution of their capillary field. Accompanying this, and probably causing it, are the diseased arteries. To appreciate these vascular changes we have but to compare the condition of the skin of an elderly man with that of a youth. In the latter the skin is of a thick velvety consistence, well supplied with blood; in the former case the skin is thin and attenuated, sometimes resembling tissue-paper and almost bloodless." [14]

The absence of these nutritional changes in cases of thromboangiitis obliterans not complicated by arteriosclerosis, and in certain elderly individuals showing marked beading of the radials, strongly suggests that intimal changes in the smaller arteries, rather than thrombosis of a large artery or medial degeneration with intimal thickening causing partial occlusion, are responsible for peripheral atrophic changes in arteriosclerosis. In thromboangiitis obliterans intimal changes are absent in the small arteries and a good collateral circulation develops following thrombosis of a larger artery. Even if one admits that a gradual narrowing of the lumen of the larger arteries develops from intimal thickening, one cannot explain the poor collateral circulation that is characteristic of the arteriosclerotic type of peripheral vascular disease without taking into account some additional factor, such as intimal thickening of the smaller arteries, which would cause a definite diminution in the blood flow to the muscles and the skin. Further, the incidence of intermittent claudication should be much higher in arteriosclerosis than in thromboangiitis obliterans, owing to the poorer collateral circulation in the former, but such is not the case. For these reasons, it would appear that partial occlusion of the smaller arteries rather than occlusion of the larger arteries is the chief and primary cause of the arteriosclerotic type of vascular disturbance.

The arteriosclerosis of advancing years and that associated with diabetes mellitus are apparently of the same type and affect vessels of the same size. While this is true, there is a difference between the skin of the patient who develops signs of peripheral arteriosclerosis during diabetes mellitus and the skin of one who develops diabetes mellitus after definite signs of peripheral arteriosclerosis have appeared. When diffuse atrophic changes are found in the skin of an arteriosclerotic diabetic, one may conclude that the diabetes mellitus was a later development. In the majority of diabetic patients, however, these advanced changes are absent and the skin over the dorsum of the foot is normal for the age of the patient. On the other hand, the skin over the dorsum of the toes, more commonly the great and second toes, may be found to be slightly thickened, wrinkled and less elastic than normal; or more marked thickening along the nail fold or under the end of the nail may be present, with the nail brittle and thickened. Calluses over the ball of the foot are not uncommon. These changes are the early nutritional manifestations of peripheral arteriosclerosis and minimal traumata

are the likely cause of their local distribution. After a slight abrasion, often caused by paring a corn or callus, infection develops; thrombosis of the small arteries occurs, causing necrosis and gangrene. In diabetic gangrene pulsation of the dorsalis pedis is usually present.

In the senile arteriosclerotic, the nutritional changes in the skin described above may be accompanied by increasing intolerance to cold and acroparesthesia. On palpation, pulsation in the dorsalis pedis is diminished or absent. Complaints of fatigue or aching pains in the legs with exercise, or crampy pains occurring more often during the night are not infrequent. Intermittent claudication, that is pain on exercise and quickly relieved by rest, occurs but, in our experience, is not commonly complained of by the patient. With progressive occlusion of the small arteries of the foot, the process may terminate in a dry, withering gangrene of part of the foot. Repeated minimal traumata from exposure to cold, hot water bottles, ill fitting boots, slight crushing, etc., would appear to be the factors causing the localization of the necrosis and gangrene to one or more toes or a small portion of the foot. If the trauma is more severe, or if infection develops through a small abrasion, thrombosis of the partially occluded arteries develops and a moist gangrene is the result. Should a large artery become thrombosed, persistent pain usually develops near the site of the occlusion; the distal parts become cold, pale or cyanosed and, with the lack of development of an effective collateral circulation, a large area of gangrene appears.

In all types of obliterative vascular disease, students of the subject stress the importance of mild external trauma as a precipitating factor in the development of gangrene, and in the treatment of diabetes mellitus special attention is given to the care and protection of the feet as a means towards its prevention. More severe trauma may injure even healthy tissues and cause thrombosis of small arteries and capillaries, but whether the results of minimal traumata on parts with a defective circulation are due to further damage of tissues or vessels, or both, has not been determined. In the obliterative type of vascular disease, the suggestion has just been advanced that repeated minimal traumata, of a type and severity to cause no disturbance to a digit with normal circulation and sensation, are responsible for the localization of gangrene to one or two digits in a foot in which there is diminution in the blood supply to the whole foot. It is a significant fact that, not only in the obliterative type but in the vasospastic type of vascular disturbance, one or two digits are apt to be more severely affected than the other three. In Raynaud's disease, the bilateral and often symmetrical distribution of the vasospastic disturbance is recognized. Nevertheless, one or more digits usually show more marked changes than the others, and following sympathectomy recovery in these is less complete or less permanent. Is it possible that repeated minimal traumata, chiefly due to exposure to cold, are responsible for the localization of the more severe changes found in certain digits in Raynaud's disease? Recently Lewis has challenged the original and generally accepted view of Raynaud that this disease is a vaso-

neurosis and that the vasospastic disturbances are due to a fault in vasomotor innervation of distant rather than of local origin in the part affected. From his carefully controlled experiments on cases of Raynaud's disease, Lewis came to the conclusion that spasm of the vessels is due, not to abnormal vasomotor impulses, but to a local vascular fault. In milder forms this defect is expressed as a susceptibility to enter a state of spasm: in the more severe forms, spasm is reinforced by local structural change. In referring to the primary cause of the spasm, he states: "In searching for the determining cause of spasm, we must review the several possibilities and ascertain whether the abnormality is local or lies at a distance; it will not be found in both. Our conclusion is that the cause is a local cause." Lewis admits that vasomotor impulses play a part in the vasospastic disturbances, but contends that the effect is due to the action of normal rather than abnormal impulses in a vessel with a local vascular fault, the exact nature of which is at present unknown. In an attempt to test these two hypotheses, Levy-Simpson, Brown and Adson [15] investigated eight cases of Raynaud's disease, using methods similar to those of Lewis. They concluded that the preponderance of their experimental evidence confirmed Raynaud's original view of the abnormality of the sympathetic nervous system. In one of the eight cases studied, a primary local vascular fault could not be excluded as the cause of the vascular spasm. As pointed out by these authors, Lewis' evidence of a local vascular fault as the primary cause of spasm has been based chiefly on experimental observation on cases of Raynaud's disease affecting the upper extremities and showing definite nutritional changes or gangrene of the tips of the fingers. It is generally recognized that the clinical results following sympathectomy in Raynaud's disease are more satisfactory in the lower extremity than in the upper, and better and more complete in mild than in severe forms of the disease. More evidence of a local vascular fault in mild forms of Raynaud's disease is necessary, therefore, before this can be accepted and a vasomotor origin discarded as the primary cause of spasm.

The observations of Stopford and Telford on cases of cervical rib with unilateral vascular complications should not be overlooked in a consideration of the primary cause of vasospastic disturbances. Some years ago, Stopford [16] reported that paralysis of vasomotor fibers never seemed to induce vascular changes but that partial division and irritation of peripheral nerves had been found on several occasions to be succeeded by vascular changes. The vascular lesion found was a thickening of the intima, most marked in the smaller arteries in the distal part of the extremity. More recently, Telford and Stopford [17] have demonstrated, to their own satisfaction at least, that the vascular complications of cervical rib are due to irritation of the vasoconstrictor fibers in the lower branch of the brachial plexus. Stopford states that he is convinced that long continued irritation of the vasoconstrictor fibers is the primary cause of the changes in the arterial wall. These observations have a double interest in suggesting that long continued irritation of vasoconstrictor fibers may be the cause, not only of vasospastic

disturbances similar to Raynaud's disease, but of the development of structural changes in the arteries. While it is impossible at the present time to express any final opinion as to the primary cause of spasm in Raynaud's disease, it is agreed that spasm of the smaller arteries is the primary cause of the vascular disturbances. It would appear reasonably certain that structural changes in the vessels are responsible for the advanced nutritional changes characteristic of the more severe forms of Raynaud's disease. No adequate explanation has been offered for the appearance of more marked changes in certain digits. The suggestion that repeated minimal traumata are responsible seems a reasonable one.

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THE DIAGNOSTIC USE OF IODINE IN THYROTOXICOSIS*

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THREE years ago at the Minneapolis Meeting of the College a paper was presented by the author on the use of iodine in exophthalmic goiter.[1] The discussion then centered chiefly about the therapeutic use of that agent. However, because of its utterly characteristic action in thyrotoxicosis the use of iodine may also give diagnostic information of great importance, in cases where the presence or absence of thyrotoxicosis is in doubt.

The chief questions which a doctor must decide, when confronted with a patient with a goiter, are whether this goiter is accompanied by hyperfunction, whether it is causing pressure, or whether it is malignant, premalignant, or inflammatory.

The symptoms of hyperfunction are familiar to you, and ordinarily the diagnosis of this disturbance is thoroughly simple. However, this is not always so. A number of conditions may resemble mild thyrotoxicosis, and in such cases single or scattered determinations of the basal metabolism may fail to prove whether thyrotoxicosis is truly present. In this class come patients with goiter which may be either colloid or hyperplastic, and with symptoms which may be due either to hyperthyroidism or to psychoneurosis. The older writers had much to say of atypical types of Basedow's disease. *Formes frustes* was the euphonious name given them. It is our belief that cases running an atypical course throughout are rare. However, when the disease is just beginning the picture may be sufficiently incomplete to cause confusion; and it is true also that in the older patients with toxic goiter the symptoms may suggest heart disease far more than thyrotoxicosis. In all of such cases the diagnostic use of iodine is helpful. It has also been stressed in the literature that tuberculosis may present a picture like mild thyrotoxicosis. This problem in differentiation, however, has not loomed large in our own experience at the Massachusetts General Hospital.

I may also mention the great group of patients who have received treatment, either surgical or roentgenological, for known toxic goiter, and who, following such treatment, may or may not have a remnant of thyrotoxicosis smouldering on. A diagnostic test with iodine in this group is often decidedly helpful in the accurate estimation of the clinical status. Indeed we have taken the stand that the final criterion of complete cure in toxic goiter is freedom from symptoms, and a metabolic rate not above standard, which is uninfluenced by iodine.

Diagnostic tests with iodine for all these purposes we have made with steadily increasing frequency in our clinic. I should like to illustrate to you

* Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.
From the Thyroid Clinic of the Massachusetts General Hospital.

some of the ways in which they have been helpful. First of all the importance of accurate observation must be emphasized. Single or infrequent determinations of metabolic rate in these doubtful cases tell us very little. It has been found necessary to establish levels of metabolism, to determine trends.

Our conception of the action of iodine in toxic goiter has been stated before. It is that at any one moment iodine diminishes, to a certain extent, the intensity of the toxemia. It has no effect on the duration or direction of the disease.

We may represent diagrammatically the metabolic effects which might occur in untreated toxic goiter upon the giving of, and omitting of, iodine medication as in figure 1. Here a prompt fall in basal metabolic rate is

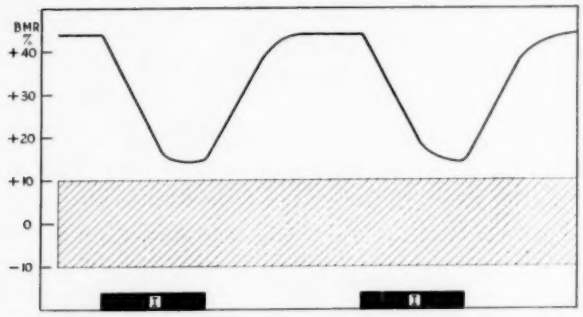

FIG. 1. Diagrammatic representation of the effect of iodine in thyrotoxicosis of moderate severity.

shown upon the giving of iodine, followed by a rise when the drug is stopped. When iodine is given and omitted for the second time the events are repeated.

In figure 2 much the same thing is depicted, only in this diagram the dis-

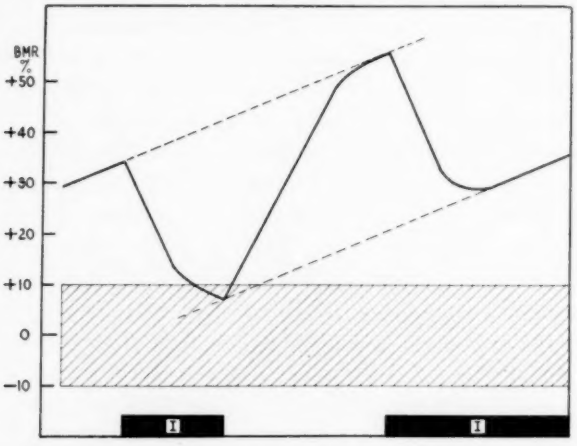

FIG. 2. Diagrammatic representation of the effect of iodine in thyrotoxicosis at a time when the disease is increasing in intensity. The upper interrupted slanting line indicates the trend of intensity of thyrotoxicosis when the patient is not receiving iodine, the lower interrupted line the trend when the patient is under full iodine control.

ease is represented as on the upward course so that when iodine is omitted there is a rise of metabolism to a higher level than that obtained before it was given, and when it is given for a second time the level reached is not as low as that reached in the first administration.

These two diagrams merely represent the usual iodine relationships. There would seldom be any necessity for a diagnostic test with iodine with the initial basal metabolic rate lying at the level shown. Let us pass, however, to figure 3. Here we have at the start a basal rate little, if at all, above

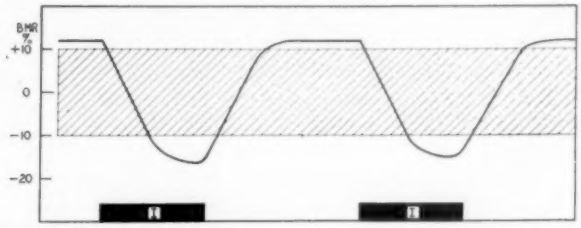

FIG. 3. Diagrammatic representation of iodine relationships in a case of genuine thyrotoxicosis but with initial metabolism little if at all above the standard zone. The fluctuations are diagnostic of thyrotoxicosis although the actual initial level would not be diagnostic of that state.

the standard level. The diagnosis is in doubt. Iodine is given. The metabolism falls to slightly below standard. Iodine is omitted. Metabolism rises to the previous level. Iodine is given again and omitted again. The events are repeated. Such fluctuations, in relation to iodine, may be taken as final proof of the existence of thyrotoxicosis, even though the rate never rises above what we call standard.

Figure 4 represents the same events taking place after operation, proving

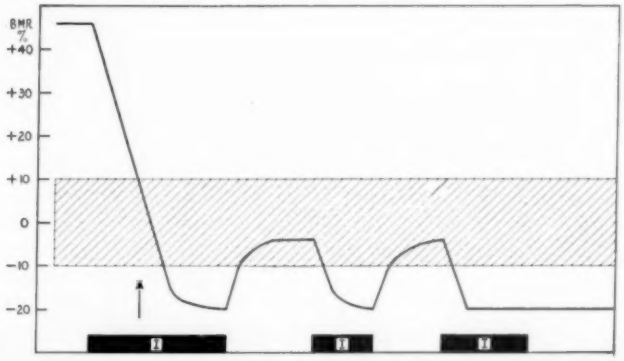

FIG. 4. Diagrammatic representation of iodine fluctuations following operation with a rate never exceeding normal. Time of operation is indicated by the arrow. Fluctuations prove that there is an element of active thyrotoxicosis still present.

that an element of thyrotoxicosis remains. Finally the time comes when no rise occurs when iodine is stopped. When this happens thyrotoxicosis has ceased, just as in rheumatic infection when no rise of temperature, white cells, or return of symptoms occurs when salicylate is stopped, we consider that active infection is over.

I should like to devote the rest of the space to some actual examples of the value of the diagnostic use of iodine.

First, an Italian girl of fifteen (Mary G.) with, when first seen, a goiter which we took to be colloid, and not much in the way of symptoms. (This case has been presented in detail in another paper.[2]) The basal metabolism had a level not above normal. My colleague, Dr. J. Lerman, was impressed with the hardness of the gland. He believed it had the feel of hyperplastic tissue. We gave iodine. The basal metabolic rate dropped 27 points. We omitted it and the basal metabolic rate rose to the previous level. We gave iodine again, got a second drop, took out the thyroid and found it hyperplastic. The test with iodine made the diagnosis here. It is interesting that it was first suggested by the feel of the gland. Here then was a patient with genuine thyrotoxicosis and yet a "normal" level of metabolism.

The next case is also that of an Italian—a married woman who was nineteen years of age when we first saw her in January 1927 (Mrs. T.). At that time there were some symptoms of slight nervousness and sweating and a slightly full, soft thyroid without other signs. Our impression was colloid goiter. She reported for observation in June of that year and we could find no clinical evidence of thyroid disease.

She turned up again in July 1930. She had had a psychic trauma and claimed to be very nervous but we could find very little evidence suggesting thyrotoxicosis. The basal metabolic rate on two occasions was in the plus twenties. (Figure 5.)

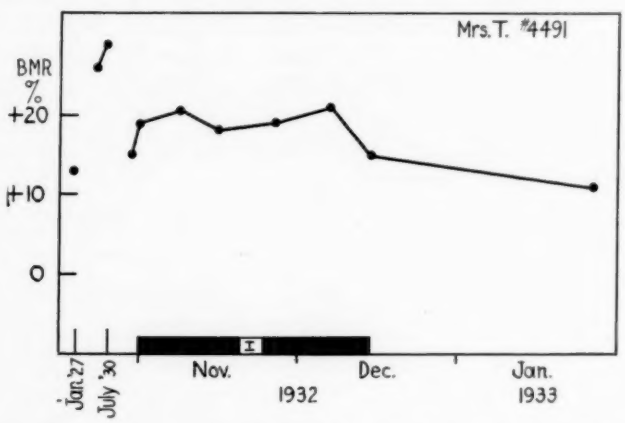

FIG. 5. Diagnostic test with iodine in the case of Mrs. T. Result negative.

We did not see her again until this winter (1932–1933). She had had a baby between visits. She claimed to be a bit nervous and to feel hot—nothing more. There was a very questionable staring look of the eyes and a soft thyroid as before. Very slight tremor was present—no other signs. The basal metabolic rate was plus fifteen.

We decided upon a diagnostic test with iodine because of the slight elevation of the rate. The result is shown in the chart—a flat negative. We believed this ruled thyrotoxicosis out. Five weeks later the basal metabolic rate had dropped to plus eleven without further treatment and the symptoms were unchanged. The original impression of colloid goiter thus proves to be correct. The symptoms are not of thyrotoxic origin. They require treatment directed toward the nervous system, not the thyroid.

We may now consider to advantage a once shell-shocked veteran of thirty-six (Mr. S.) who was first seen in our clinic in November 1931. He had had symptoms

of nervousness, exhaustion and trembling ever since the war. A goiter had been noted the year before. On physical examination we found moderate bilateral exophthalmos, stare and lid lag, and a slight, soft, symmetrical enlargement of the thyroid without bruit. His basal metabolic rate was plus twelve. We thought he had the remnant of a smouldering Graves' disease of long standing.

Followed over a period of three months without iodine the basal metabolic rate was found to fluctuate somewhat but showed no steady trend either up or down and did not average above the standard zone. (Figure 6.) Then on iodine for seven months it did the same. The chart shows not the slightest evidence of an iodine re-

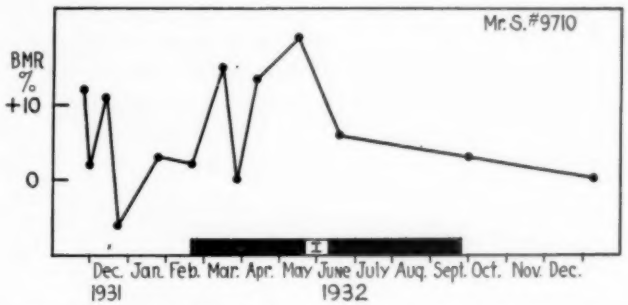

FIG. 6. Diagnostic test with iodine in the case of Mr. S. Result negative.

sponse. He is exactly as well off without iodine as with it, both metabolically and symptomatically. He may have had exophthalmic goiter in the past and some exophthalmos remains but he is not thyrotoxic now. The problem for therapeutics is psychologic not endocrine.

Another case of considerable interest (Mr. K.) that has lately come to our attention is that of a business man of sixty-two who began to suffer from undoubted thyrotoxicosis at the beginning of last summer. His symptoms at the onset were subdued and on August 9, 1932 his basal metabolic rate was only plus sixteen. We had not control of his treatment and his own physician elected roentgen-ray treatment and iodine rather than operation which we would have advised. On this regime he improved, though on October 25, 1932 his basal metabolic rate was plus eighteen. During the course of the roentgen-ray treatment, although improving symptomatically in other ways, he developed exophthalmos which had not been present before. On January 14th, still on iodine, the course of roentgen-ray complete, he had a basal metabolic rate of minus twelve and felt well in every way except that his eyes were very irritated and becoming increasingly so. We omitted iodine and in eleven days the basal metabolic rate rose to plus five and symptoms of nervousness returned.

The situation was that the patient had been relieved of all symptoms except ocular ones on a regime of iodine and roentgen-ray. His basal metabolic rate was entirely within standard limits even off iodine. His goiter was very small and firm; his eyes were getting steadily worse. We were worried about his eyes. We believed that the rise in basal metabolic rate and increase in symptoms which took place when he was released from iodine control proved that an element of thyrotoxicosis still lurked, and we advised subtotal thyroidectomy in spite of his low metabolic rate, on account of his eye condition, although we would have been content to carry on with an expectant program had this not been present. I cannot tell you of the outcome for he is now undergoing preparation for operation.*

* Subtotal thyroidectomy was done on February 6, 1933. The gland removed showed hyperplasia typical of exophthalmic goiter. Iodine has been continued ever since, and the basal metabolic rate has dropped to a level in the neighborhood of minus twenty. In spite of this, the exophthalmos and ocular irritation persist and seem truly malignant.

I will present just one more case in which the test with iodine ruled thyrotoxicosis out. A married German machinist of forty was seen for the first time last September. His illness had covered eighteen months; the symptoms were excessive sweating, palpitation, precordial pain, dysphagia and nervousness. At the same time there had been progressive exophthalmos in the left eye. His right eye was of glass. His thyroid was small but palpable and rather firm. There was no thrill or bruit. He had a tremor of the fingers and fibrillary twitchings over his muscles, but no marked atrophy. The left eye though prominent showed no lid lag. His basal metabolic rate was plus nine. It was thought that exophthalmic goiter was probably present and he was admitted to the hospital. The next basal metabolic rate showed a rate of plus thirty-eight, but this was an isolated reading. The rest were between plus two and plus thirteen. On iodine there was no trend either up or down. (Figure 7.) It was concluded that he had no thyrotoxicosis and he was discharged.

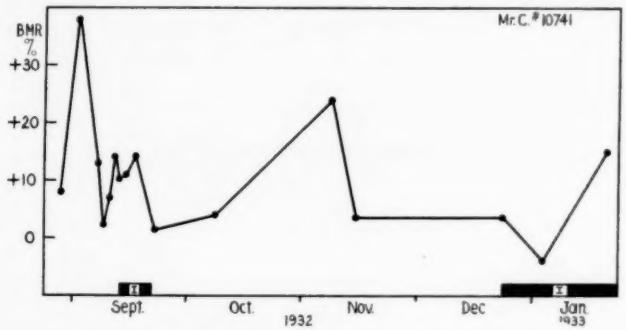

FIG. 7. Diagnostic test with iodine in the case of Mr. C. Result negative.

Subsequent events have borne this out. There was one more isolated high reading but two others close to the zero line. A second trial with iodine showed no consistent change either way. Furthermore no improvement in symptoms when taking the drug was noted by him either time. This is as important as is the lack of change in metabolic rate. Truly thyrotoxic patients nearly always testify spontaneously to marked improvement while they are receiving iodine and to feeling worse when it is stopped. The cause of his exophthalmos remains in doubt. Of course he may return to us in the future with definite exophthalmic goiter but the test convinces us that he does not have it now.

In conclusion then I will repeat that in iodine we have an agent helpful in the diagnosis of thyrotoxicosis as well as in the treatment thereof. Whenever there is any doubt or question of its presence the effect of iodine should be observed. Isolated basal metabolic rates are not enough. Sufficient data to observe definite levels and trends must be obtained. The absolute level is of little significance. The fluctuation is what counts. A drop from plus nine to minus eight with iodine and return to plus nine when the drug is stopped is significant. When thyrotoxicosis is truly present, even though in slight degree, the response to iodine is definite, delicate and exact.

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SCHIZOPHRENIA FROM THE PHYSIOLOGICAL POINT OF VIEW*

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The schizophrenic psychosis, of all unsolved problems, presents to the medical profession the outstanding challenge of our day. This disorder alone fills one-fifth of all hospital beds in the United States. It is presumably equally prevalent in other parts of the world. Its cost is incalculable. Its onset is commonly in the early years of maturity and it persists to a greater or lesser degree of severity throughout a lifetime that is not greatly curtailed. To the patient it represents exclusion from family and friends—literally in many cases, spiritually in any case. It casts a pall of undeserved stigma upon the entire family in which it strikes, and no family is exempt. There is probably no other disorder known to medicine that exacts so great a cost in prolonged unhappiness as does schizophrenia.

No more can the monetary cost be calculated. In our country approximately one hundred and fifty thousand able-bodied citizens are removed from productive pursuits to be maintained in special institutions. In Massachusetts the average period of hospitalization is about eleven years. In addition to the hospitalized population there are probably as many schizophrenics outside of institutions who contribute relatively little to society. At best they are inoffensive incompetents and at worst they constitute a portion of the criminally insane with hobos, prostitutes and other less offensively queer people falling in between.

Numerous items go to make up the toll of the social loss from the disorder. The hospital victims are expensive to maintain. In the United States the total investment in buildings for their care amounts to nearly a half billion dollars. Interest charges and depreciation on the buildings and their equipment are heavy and increasing items. In addition there are all the various maintenance costs—food, clothing, professional services, etc. The cost of the non-hospitalized group can only be guessed at but it must be a very considerable drain on families and on social agencies. From careful consideration of such cost items as are known and conservative estimate of others, the loss from this disorder appears to be in excess of a million dollars a day and estimates of twice that sum have been made.

Schizophrenia is as varied in its individual manifestations as is human nature itself. Under one name or another it has been known from the beginning of medical history. The schizophrenic picture can be recognized in the devil-possessed people of biblical and medieval times. The witchcraft delusion would seem to have amounted largely to a panic-stricken, confused recognition of the existence of schizophrenia. It remained, however, for Kraepelin only a generation ago to delimit the psychosis as an entity under

* Read at the Montreal Meeting of the American College of Physicians, February 9, 1933.

the designation of dementia praecox. Of late years Bleuler's term, schizophrenia (split mind) has largely come into use as more accurately descriptive of the disorder. Actually, the patient does not necessarily become demented nor does the disorder always show early onset, as Kraepelin's designation implies.

In modern psychiatric thought schizophrenia, or perhaps more accurately, the schizophrenic reaction, consists of two fundamental deviations from normality, together with an assortment of secondary features that give a kaleidoscope variety to the individual clinical pictures. Bleuler's primary characteristics are disorders of the association processes and a partial loss of contact with reality that is indicated in the term schizophrenia itself. Scarcely less characteristic are disturbances of the emotions. From the point of view of the physiologist, Kraepelin's definition of the psychosis as "a peculiar disorganization of the inward coherence of the psychic personality with predominating damage to the affective life and will" seems particularly suggestive.

The psychosis presents a bizarre mélange of psychologic normality and abnormality. Memory and orientation tend to be well preserved. The patients often show little disturbance of apprehension. Despite frequent appearances to the contrary, they are usually rather well aware of what goes on about them. Many pages would be required to present even an elementary account of the manifestations of the disorder. We may mention only hallucinations, delusions, poor judgment, incongruity of emotions—commonly with apparent neutrality or indifference—incoherence in train of thought and displacement of normal volitional responses by automatic or impulsive reactions. Bizarreness of conduct is seen in infinite variety.

Jung and numerous other writers have commented on the resemblance of the schizophrenic psychosis to the normal dream state. It differs from your dreams and mine mostly in that upon awakening from sleep the dream is not dismissed and in that the activities of the dream are largely carried out rather than merely visualized. The schizophrenic state and the dream state are strikingly similar in the free use of symbolism. Things do not mean what they seem but what they signify in the patient's own particular code. If the reader will imagine that he had been awakened from a vivid dream but that as he went about his daily affairs the dream continued to occupy the greater part of his attention, to dominate his thought and his activity, he will have a sufficiently accurate picture of schizophrenia for purposes of this discussion. Largely it is a manifestation of more or less disguised wishes or fears masquerading as accepted reality.

To one studying the phenomenology of schizophrenia from the physiological point of view the first question that presents itself is this: Could the manifestations of the disorder arise from organic causes or must we seek for some mysterious "dynamic" influence, an unresolved Oedipus complex or what not? Unquestionably earlier emotional experiences play an important rôle in the coloring of the individual picture, but are they necessarily concerned in the genesis of the psychosis itself?

The answer would seem to be clearly in the negative. Point for point, the individual symptoms can be paralleled from conditions that are clearly organic in origin. In our dreams we are all rather schizophrenic, and perhaps no more mysterious etiology is involved here than depressed oxygen consumption in the brain cells. The victim of chronic alcoholic intoxication may show hallucinations and delusions quite as striking as those of the schizophrenic. The rich imagery of acute morphine intoxication and especially the hallucinations of mescal poisoning are phenomena of the schizophrenic order. Even the motor manifestations of catatonic dementia praecox can be closely simulated by the administration of bulbocapnin. In the perennial debate between the organicists and the psychogeneticists the fact is frequently overlooked that the individual symptomatology of schizophrenia can be duplicated in almost every particular by the manifestations of dementia paralytica. In this latter psychosis we seek for no more mysterious causation than the syphilitic organism. Were the fact not known that dementia paralytica is caused by syphilis the literature would no doubt be quite as full of "dynamic" analyses and speculations as is that devoted to schizophrenia, and we might still be seeking in them the primary cause of the disorder.

Schizophrenia, then, could be caused by strictly organic factors. As a matter of fact, does the evidence compel us to assume an essential organic element in the causation? The disorder shows a striking predilection for individuals of "tainted heredity" and those of dysplastic constitutional types. Our most instructive single datum is the comparative double incidence of schizophrenia in identical as compared with ordinary, fraternal twins. Unfortunately the data are not yet sufficiently numerous to be entirely compelling but so far as they go they indicate that if one of a pair of identical twins develops schizophrenia his fellow twin has relatively little hope of escaping, whereas if one of a pair of fraternal twins develops the disorder his fellow is in no special danger. Identical twins are organically two parts of the same individual, whereas fraternal twins are quite as dissimilar as are other children of the same family. Organically the two types of twins are entirely different but there is no reason to assume that the emotional experiences of the two sorts are particularly different. These three categories of facts seem to allow no escape from the conclusion that organic factors are important in the chain of causation whether or not they are invariably operative. This is true irrespective of what weight one may assign to psychogenic factors. Apparently, then, the individual develops schizophrenia primarily because he was born to have it. If this conception is true the most important question confronting the investigator is: What is organically peculiar about the schizophrenic?

During the past five years my collaborators and I at the Worcester State Hospital have been attempting to learn as precisely as may be the answer to this question. During this period some 300 cases have been rather elaborately studied, not only as regards their psychologic and psychiatric char-

acteristics but especially their physiologic. The outstanding result of the first four years' work was to demonstrate in the individual patient a remarkable degree of variability of the physiologic functions from one test to another. So troublesome had this feature of variability become that last year we decided to devote the entire resources of the research service to a study of the variability, as such. This engaged the entire time of some 50 or 60 people, including nurses and attendants, for about a year.

Each patient received a detailed physical examination to eliminate organic disease that might serve as an unnecessary complication of the problem. Any one showing other than minor passing ailments was rejected. A detailed social history was compiled for each patient. He was given an intensive psychiatric study to insure that he was actually suffering from schizophrenia. He was then subjected to seven months of intensive investigation following the schedule set forth in the accompanying table. (Table 1.) After a month of study by this schedule he had a two months'

TABLE I

Schedule

	First Week	
Monday	9:00 a.m. Psychometrics.	1:00 p.m. Physical and psychiatric examinations.
Tuesday	9:00 a.m. Psychometrics.	1:00 p.m. Physical and psychiatric examinations.
Wednesday	9:00 a.m. Psychometrics.	1:00 p.m. Physical and psychiatric examinations.
Thursday	7:30 a.m. "Basal metabolism" including rectal temperature, pulse, blood pressure, weight, height. Blood samples collected for quantitative analysis and phytotoxic test. 9:30 a.m. Breakfast.	1:00 p.m. Psychiatric examination.
Friday	7:30 a.m. "Basal metabolism." 9:30 a.m. Breakfast.	1:00 p.m. Diagnosis by admitting staff. Psychiatrist's note.
Saturday	7:30 a.m. "Basal metabolism."	p.m. Mental note.
	Second Week	
Sunday	a.m. Rest.	p.m. Rest.
Monday	9:00 a.m. Experimental psychology.	1:00 p.m. Psychiatric ward observations. 3:00 p.m. Photography — 2 nude poses.
Tuesday	9:00 a.m. Experimental psychology.	1:00 p.m. Psychiatric ward observations.
Wednesday	9:00 a.m. Experimental psychology if not previously completed.	1:00 p.m. Psychiatric ward observations.
Thursday	8:00 a.m. Oculo-cardiac test. 9:30 a.m. Breakfast.	1:00 p.m. Psychiatric ward observations. 1:30 p.m. Dental examination and x-ray studies of skull, chest, and gastrointestinal tract.
Friday	a.m. Blood volume, plasma volume, hemoglobin, blood gases, blood pH, blood morphology.	3:00 p.m. Schneider Test of cardiovascular efficiency. Psychiatric ward observations.
Saturday	8:00 a.m. Rest period. Recheck of Friday if necessary.	p.m. Rest.

TABLE I—(*Continued*)

	Third Week	
Sunday	7:00 a.m. Start 24-hour urine collection.	p.m. Urine collection.
Monday	7:00 a.m. Finish urine collection. 8:30 a.m. Inject phenolsulphonephthalein. Collect specimens.	2:30 p.m. Blood pressure.
Tuesday	7:00 a.m. Start collection of 24-hr. urine. 7:30 a.m. "Basal metabolism," "Lung volume." 9:30 a.m. Breakfast.	1:00 p.m. Psychiatrist's note.
Wednesday	7:00 a.m. Complete 24-hr. urine collection. 8:30 a.m. Inject phenolsulphonephthalein, collect specimens.	
Thursday	5:00 a.m. Galactose tolerance control sample. 6:30 a.m. Collect samples for blood chemistry and blood morphology. 7:00 a.m. Galactose tolerance test.	1:00 p.m. Psychiatrist's note.
Friday	5:00 a.m. Repeat galactose tolerance test.	1:00 p.m. Psychiatrist's note.
Saturday	5:00 a.m. Repeat galactose tolerance test.	1:00 p.m. Psychiatrist's note.
	Fourth Week	
Sunday	a.m. Rest.	p.m. Rest.
Monday	8:00 a.m. Fluoroscopic gastrointestinal studies begun. Psychiatrist's note. Internist's note on physical status.	p.m. Gastrointestinal series.
Tuesday	a.m. Gastrointestinal studies continued. Psychiatrist's note.	
Wednesday	Gastrointestinal studies continued. 8:00 a.m. Blood sedimentation test. Bromsulphonephthalein test for liver function. Psychiatrist's note.	
Thursday	Gastrointestinal studies continued.	p.m. Psychiatrist's note.

rest period during which, however, certain accessory tests of the cerebrospinal fluid, of the reactions to various drugs that act on the autonomic nervous system, and of the liver functions were made. The studies of the main schedule were then repeated, another rest period was interposed and finally a third month of study was carried out. Many of the tests were made in duplicate and some in quadruplicate, hence at the end we had from three to twelve tests on each patient. Some 65 patients have now been through the entire series of tests but this report will be based largely on the tabulated results obtained in the first 54 patients of the series.

Suffice it to state that in many of his physiologic activities the schizophrenic is strictly normal, though perhaps unusually variable. Attention will be directed mostly to those features in which abnormality proved to be characteristic.

The Urine. The urine was strikingly normal as regards total solids, total nitrogen, nitrogen partition and microscopic residue. Just as striking

was its abnormality as regards volume. The individual variability in this respect was high but the average volume for the series was about twice the normal amount. Table 2 sets forth the results that were obtained in 26

TABLE II

Urinary Volume

	Min.	Max.	Range	Mean	Stand. Dev.
Normal subjects (26)	655	2805	2150	1328 ± 83	629 ± 59
Schizophrenic subjects * (44)	510	8000	7490	2602 ± 120	1851 ± 85

* All catheterized.

normal subjects as compared with those of 44 patients from whom the specimens were obtained by catheter. The most striking features of the table are that the average output of the patients was 2602 c.c. per day as compared with 1328 for the controls and that the variability was about three times as great. The total solids being normal and the volume high the specific gravity was of course correspondingly low. In individual cases we have often obtained volumes from three to eight liters per day. In 48 of the 63 patients studied to date the average volume was above the conventional high normal of 1500 c.c. These findings were entirely unexpected and their significance is by no means clear. They suggest either a high incidence of disturbed function of the diencephalon or of the posterior lobe of the pituitary gland. They prove that in at least one respect the average schizophrenic patient is quite as abnormal physiologically as he is psychologically.

Blood Chemistry. The chemical constituents of the blood were also for the most part strictly normal on the average but they also showed a rather high variability. The blood cholesterol averaged slightly low as compared with findings in a control series of 24 subjects but the variability was so great as to cast some doubt upon the validity of the difference. The blood gases and blood pH were normal on the average and showed about a normal range of values with the exception of the venous oxygen which in individual cases was strikingly low.

Blood Morphology. The various blood counts were found to show a normal range in most respects, but a slight secondary anemia ran through the picture, being seen in fairly well marked degree in more than half the cases. The average red cell count was 4,957,000 which, for adult males, is slightly low. The total white cell count, as many other observers have noted, was somewhat high, the average being 10,477. The variability from patient to patient and in the same patient from period to period was notably great.

Gastrointestinal Motor Functions. The motor functions of the upper gastrointestinal tract were quite normal as determined by roentgen-ray studies following barium meals. In the colon, however, considerable stasis was found to be characteristic, the average emptying time being 74 hours.

Carbohydrate Metabolism. The fasting blood sugar was strictly normal both in its average, namely, 96 mg. per 100 c.c., and in its range. We

have not studied the reaction following ingestion of glucose or the injection of adrenine but the evidence in the literature indicates a frequent prolongation of the hyperglycemic curve. We used as an index of the carbohydrate metabolism the galactose tolerance as recommended by Rowe. This was found to be highly variable in the individual patients but the average was 22 grams as compared with Rowe's average of 30.

The Liver Function. There are many features in the schizophrenic psychosis that suggest the operation of a toxic factor. One of the obvious sources of obscure metabolic intoxication is the liver. We have attempted to test the functional integrity of this organ in a variety of aspects as brought out by nearly all of the standard liver-function tests. The voluminous details are difficult to epitomize. Suffice it to state that the general trend of the evidence indicates that the liver in one or other of its functions is abnormal in a fairly high proportion of our cases. And this despite the fact that our series included a considerable number of chronic as contrasted with acute cases in which, according to other investigators, incidence of liver dysfunction is especially high.

Phytotoxic Reaction. Macht, following several earlier investigators, has described a method for the detection of metabolic toxins by use of seedlings of the plant *Lupinus albus.* Looney and Macht were able to show that the blood of patients presenting marked depression is definitely toxic to these seedlings, just as Macht reported the blood of menstruating women to be. We had hoped by this technic to discover some evidence of the long-sought schizophrenic toxin, but the results were negative. If the schizophrenic is characteristically a victim of metabolic intoxication the toxin either works so slowly and at such low concentration as not significantly to affect the growth of *Lupinus albus* or else it is of a nature to which this plant is immune. Parenthetically, in view of the emphasis that Holmes and others have placed upon colonic "auto-intoxication" as a cause of schizophrenia it is interesting to note in passing that our patients, despite a high incidence of stagnation in the lower bowel, have seldom showed indicanuria.

Respiratory Complex. Perhaps the most striking abnormality in the metabolic picture of schizophrenia as we have seen it is in the composite group of findings relating to respiration, in the broad sense. The patients as a group showed a characteristic hypometabolism. The basal blood pressure averaged about 100; the basal pulse rate, 59; and the average oxygen consumption rate, 89 per cent of standard normal. The average weight was found to be 62.6 kg. which for the age and height was about 16 per cent below prediction. By way of illustration, in table 3 are presented the chief elements in the respiratory complex of an individual subject as determined on 12 different occasions over the course of seven months. The clinical condition of the patient showed relatively little variation within this time, hence the findings need not be discounted as mirroring a fluctuating psychosis. The data are more than commonly satisfactory, too, in that the patient was in good nutrition throughout the period of study.

TABLE III

Respiratory Complex

	First Period	Second Period		Third Period	
	8/18/31	*11/29/31*	*11/10/31*	*1/21/32*	*2/2/32*
Weight	73.0 kg.	73.6 kg.	74.0 kg.	68.6 kg.	67.6 kg.
Lung vol. (spirometer), % of normal	94	50	60	70	98
Nutritional index, % of prediction from height-age	100	101	102	94	93
	8/5/31	*10/29/31*		*1/21/32*	
Oxygen consumption, % of prediction	97	71		66	
Blood pressure, mm. Hg	96/58	104/70		110/56	
Pulse	48–50	44–44		36–42	
Temperature, rectal	99.2	98.2		98.8	
Respiratory rate	14–15–14	15–15–14		13–14–14–14	
	8/6/31	*10/30/31*		*1/22/32* *	
Oxygen consumption, % of prediction	89	76		77	
Blood pressure, mm. Hg	122/78	96/60		98/52	
Pulse	54–52	44–42		34–38	
Temperature, rectal	99.4	98.4		99.0	
Respiratory rate	16–17–16	14–14–13		16–15–16	
	8/7/31	*10/31/31*		*1/23/32*	
Oxygen consumption, % of prediction	100	72		69	
Blood pressure, mm. Hg	116/68	94/50		98/56	
Pulse	54–54	40–40		33–35	
Temperature, rectal	99.2	98.0		98.8	
Respiratory rate	20–20–20	12–13–13		12–13–13	
	8/18/31	*11/10/31*		*2/2/32* *	
Oxygen consumption, % of prediction	81	76		71	
Blood pressure, mm. Hg	108/80	94/48		110/66	
Pulse	44–46	50–50		44–48	
Temperature, rectal	98.2	99.0		98.8	
Respiratory rate	20–24–24	12–14–16–15		10–10–11–12	

* Oxygen consumption rate 1/22/32—77%. During this test workmen overhead were making a great deal of noise. The patient was restless, wandering about the room before he could be persuaded to lie down. He said he did not want to take the test. Oxygen consumption rate 2/2/32—71%. A great deal of hammering overhead, continuous and disturbing. Patient apparently calm, however.

With the exception of two occasions on which workmen were making considerable noise overhead the determinations were all made under technically satisfactory conditions. The patient had been brought to the laboratory before breakfast and had lain quietly for a half hour before the observations were made. The table is mostly self-explanatory. Suffice it only to state that the oxygen consumption rate is expressed in terms of percentage of normal prediction, the findings being calculated to both the Aub-Dubois and Harris-Benedict standards and the average taken. Special care was observed to prevent leakage from or into the system and the use of spent soda lime was rigorously excluded by test of the reagent. Such errors as exist in the determination therefore were necessarily in the upward direction. Accordingly, if as was usually the case, the two determinations that were routinely made at each session differed from each other, the lower was selected as most nearly approximating the basal. It is probable, however, that the rate even so selected was substantially higher than the true basal.*

* The topic is further critically discussed in the following article. HOSKINS, R. G., and WALSH, A.: Oxygen consumption ("basal metabolic rate") in schizophrenia, Arch. Neurol. and Psychiat., 1932, xxviii, 1346–1364.

It will be noted first of all that the rate of oxygen consumption was strikingly variable as between the first and the other two periods and to a considerable extent within the given periods. In the first period the range was from 81 to 100 per cent of normal and in the third from 66 to 77 per cent. The nutritional level was the same in the first and second periods but there was a falling off from 101 to 94 per cent of the normal weight between the second and third periods. The blood pressure was even more variable, ranging from 94/48 to 122/78 in the various cases. It must be emphasized that the patient was lying quietly in each case with no detectable evidence of tension. The pulse under similar conditions varied from 33 to 54 beats per minute. The temperature also was slightly subnormal though not strikingly so.

The oxygen consumption rate, then, is characterized by a high degree of variability as are the associated findings. The only probable source of error in the blood pressure determination is concealed psychomotor tension of the subject. We are disposed therefore to regard the lower values, namely 94 to 98, as most representative of the true characteristic basal level.

The data would bear further discussion from several points of view but suffice it to state that the patient conformed to the trend of the entire series in showing low blood pressure, slow pulse and reduced oxygen consumption rate—all of which would be conducive to reduced level of activity of the brain cells and all of which are, as a matter of fact, conditions that are characteristic of ordinary sleep.

Emphasis must be laid on the fact, however, that the patients, although basically in a metabolically somnolent condition, retain the ability under stimulation to arouse at least temporarily to a more normal condition. Thus the same patient who was shown to have a basal blood pressure of less than 100 was found when subjected to special efficiency tests in the afternoon to show a level ranging from 115 to 132 mm.

But the approach to normality in the average case is only partial. In 200 determinations of blood pressure and pulse rates made on our patients in the mid-afternoon these features averaged significantly low as compared with those obtained by Schneider under similar conditions in 2000 tests on aviators. The differences are shown in table 4. Under moderate exercise

TABLE IV

Averages of Pulse Rate and Blood Pressure in Schizophrenic as Compared with Normal Subjects

	200 Tests on Schizophrenics	2000 Tests on Aviators
Reclining		
Pulse rate	64	74
Systolic blood pressure	112	118
Standing		
Pulse rate	81	91
Systolic blood pressure	119	120

(Courtesy of Dr. J. M. Linton)

the blood pressures of the two groups equalize but the pulse rates of the schizophrenics continue to lag.

The schizophrenic differs in his respiratory metabolism from the normal person in another important respect. One of the striking adaptive mechanisms of which we all make greater or less use in avoiding obesity is the stimulating effect of food, and especially protein food. The more protein we eat the more fuel we burn. In the schizophrenic subject this is not so, according to statistical tests. The protein food metabolised is mirrored in the total nitrogen excreted in the urine. In normal subjects according to an analysis made by E. M. Jellinek of our Staff, there is a definite positive correlation between the total urinary nitrogen and the oxygen consumption rate. In schizophrenic subjects the correlation is practically nil. This fact would seem to indicate that the schizophrenic fails to get the stimulation from protein consumption that the ordinary person experiences.

The characteristic variability of the test findings was partially illustrated in table 3. The range of some of the other findings in the same patient is shown in table 5. The table sufficiently indicates the futility of attempting

TABLE V

Extreme Values Noted in an Individual Case

Oxygen consumption rate	100 %	66 %
Blood pressure—systolic	122 mm.	94 mm.
Pulse	54	34
Temperature (rectal)	99.2°	96.6°
Urine volume	1960 c.c.	510 c.c.
Galactose tolerance	40 gm.	20 gm.
Erythrocytes	4,160,000	4,630,000
Leukocytes	15,200	10,300
Lymphocytes	42 %	18 %
Blood non-protein-nitrogen	49 mg.	32 mg.
Blood sugar	116 mg.	88 mg.
Colon emptying time	168	96

to appraise the physiological status of a schizophrenic subject from single tests. As a matter of random chance the values obtained in any one examination might have fallen anywhere between the extremes noted. If more tests had been made in the case cited the range would probably have been still further extended.

According to our findings, then, the schizophrenic patient is quite as abnormal physiologically as he is psychologically. First of all, he is a very unstable person. In Cannon's parlance, his *homeostasis,* i.e., his ability to maintain a metabolic "steady state," is defective. In numerous respects the fluctuations center about normal levels but in other respects the basal levels are displaced. Apparently most fundamentally significant is the reduction in the activities having to do with body oxidation—the circulatory efficiency and the specific dynamic action of protein. The similarity of the metabolism of the resting but wakeful schizophrenic with that of the normal person in sleep is striking. Perhaps the characterization of the psychosis as

a dream state is worthy of more literal acceptance than had previously been supposed. A dreaming mind in a somnolent body appears to be the fundamental condition of the psychosis. The body, however, is rather easily aroused whereas the dream state is notably resistant to correction.

In addition to the hypometabolism, the increase in urine volume seems equally characteristic.

Which is cause and which effect? Does the psychosis cause the physiologic abnormalities or does it result from them? Or are all the recognized abnormalities joint results of some more fundamental defect? Such data as those reported fail to determine the question. The researches herein reviewed are strictly at the descriptive level and at this level causation does not emerge. The data have as their chief significance the setting of a problem for more penetrating research. Some of the specific individual questions that are raised we now have under study.

Humanity has much at stake in such researches. Many attempts have been made to find a successful cure for schizophrenia. Numerous ways of palliating the disorder are known but nothing genuinely curative. By all the teachings of medical history essentially the only hope is first to discover the cause. Then and then only can intelligent efforts at cure be devised. Only the most improbable fortunate accident will bring us sooner to the goal.

Of the millions of dollars now being expended annually for medical research on this continent, how much is being devoted to this, the greatest problem of all? One per cent would be an extravagant estimate. Compelling statistics are not available but some idea of the neglect of the problem can be obtained by noting the relative numbers of articles appearing in medical journals. In the Quarterly Cumulative Index Medicus for 1931 there are listed many thousands of articles on human diseases. Of the various disorders the list of articles on tuberculosis ran to 620 column inches; the stomach and its diseases, 214 inches; the thyroid and its diseases, 137 inches; cancer, 190 inches; while schizophrenia bulked a mere 39 inches. Perhaps the measure of our own culpability is better indicated by the fact that from all the periodical publications on the North American Continent in this same year, 1931, there were listed but 26 articles on dementia praecox in any of its aspects. And that psychosis fills one-fifth of all hospital beds.

Those stark facts speak for themselves. Medicine has put society in its debt in innumerable ways but until the researches in schizophrenia are multiplied manyfold its whole duty will not have been done. The problem is admittedly difficult but clues for its solution are available. For all that any one knows to the contrary schizophrenia may be entirely preventable or curable. To go on suffering its ravages without making a much more respectable effort than has yet been made in our own defence would seem to amount to sheer social stupidity.

Summary

A brief report is offered of the results of a five-year coöperative research program at the Worcester State Hospital on the psychosis, schizophrenia.

The disorder was found to be characterized physiologically by two sorts of deviation from normality. In numerous respects the individual patients showed marked variability from one functional test to another but in most regards the average functional level was found to be essentially normal. The average urine volume, however, was about twice that of non-psychotic subjects living in the same environment. There was a tendency to secondary anemia and moderate leukocytosis was common. The galactose tolerance averaged 22 grams as compared with a reported normal average of 30 grams. The motor functions of the colon were retarded. The complex of functions centering about oxygen metabolism was found to be characteristically abnormal. The blood pressure, pulse rate and stimulating effect of protein were reduced as was the actual oxygen consumption itself. As a group the patients were moderately underweight despite generous dietaries. Further studies as to how these abnormalities are brought about might throw significant light on the cause of the psychosis. There are suggestions that pituitary deficiency may play an important rôle.

Emphasis is laid on the fact that schizophrenia presents the outstanding medical problem of our time. It fills one-fifth of all hospital beds in the United States; its cost in money is great and in human suffering is incalculable. Practical clues are available for further study of the problem but it is receiving an almost negligible proportion of the total funds and efforts now being devoted to medical research.

EVALUATION OF THERAPY IN CHRONIC ATROPHIC ARTHRITIS*

By W. Paul Holbrook, M.D., F.A.C.P., *Tucson, Arizona*

The treatment of chronic arthritis is still passing through a phase of promiscuous therapy, much as tuberculosis did 20 years ago. There has been a tremendous increase in interest concerning rheumatic diseases during the past ten years, and, as a result, the medical literature has been flooded with reports of cures accomplished by all conceivable types of treatment. As a consequence, the majority of clinicians have been unable to separate fact from fancy. Diets, vaccines, colonic irrigations, various forms of electro-, physio-, and hydrotherapy, typhoid vaccine injections, the administration of scores of chemicals orally or by injections, endocrine therapy, postural correction, and even the manipulation of the feet, have all been hailed by the public, and too often by the medical press, as the answer to the problem of treating chronic arthritis. It is most unfortunate that many of these methods have been made available to the general profession, for some of them are not only worthless, but are instruments of incalculable harm. The many remedies offered are of course the best evidence of a lack of specificity.

In an attempt to evaluate the many therapeutic procedures, the last 1000 cases of chronic arthritis passing through the hospital and clinic of the Desert Sanatorium have been grouped according to the different types of therapy employed and have then been carefully analyzed with regard to response. The classification of chronic arthritis has been discussed in detail in previous papers. A brief outline of classification, given in table 1, will serve to identify the type under discussion.

I. *Atrophic Arthritis.* In our experience atrophic arthritis can be sepa-

Table I

Chronic Arthritis

I. Atrophic (Rheumatoid, Chronic Infectious)
   a. Without clinical evidence of infection.
   b. With clinical evidence of infection.

II. Hypertrophic
   a. Generalized of old age.
   b. Localized, the result of injury or trauma.

III. Spondylitis
   a. Without bony ankylosis.
   b. With bony ankylosis.

IV. Rheumatoid Affections
   Myositis, fibrositis, neuritis.

* Read at the Montreal Meeting of the American College of Physicians, February 10, 1933.

From the Desert Sanatorium and Institute of Research, Tucson, Arizona.

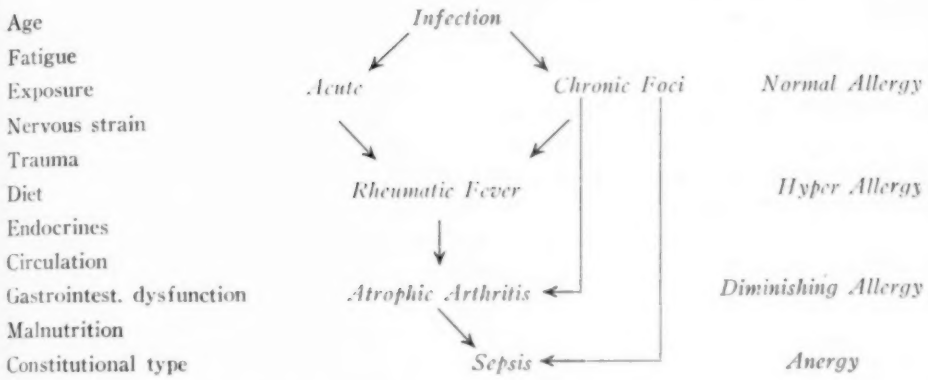
rated clinically into two general groups. The first, "*a*," is an afebrile, insidious, progressive, symmetrical, deforming, and crippling disease. It occurs most frequently in women beyond the fourth decade. It is differentiated from the second group by its symmetry, the lack of fever, the early and marked widespread demineralization, the early cartilage destruction, the trophic skin and muscle changes, and the complete failure of therapy when directed toward infection or when the problem is attacked from the standpoint of foci of infection. It is a disease often dramatically affected by the patient's emotional life and is, in many instances, related to some form of gastrointestinal dysfunction. The second group, "*b*," is characteristically what is known as chronic infectious arthritis. There is, however, in contrast to group "*a*," fever, malaise, red or hot joints, and other constitutional symptoms of infection. In its most acute phase it may resemble rheumatic fever. It should be understood that the separation of atrophic arthritis into two groups is made solely on a clinical basis and especially because of the difference in response to treatment. These groups may possibly represent only a different response to common etiological factors.

Inasmuch as chronic atrophic arthritis constitutes the real stumbling block in therapy, and because of space limitation, our discussion will be confined wholly to this group, of which there are more than 300 in this series. In reporting results from treatment, only generalizations will be offered. The reporting of results in percentages cured and improved, through the employment of a certain therapeutic procedure, has always been a source of amazement to us. Everyone who deals with such patients over long periods of time realizes that such statistics are almost entirely dependent upon the statistician. These patients in our series have been followed closely and at frequent intervals checked with regard to joint swelling and mobility, blood pressure, distribution of bone minerals, temperature range, blood count, sedimentation time of erythrocytes, pain, and general symptomatology. These were the criteria used in estimating improvement.

Our concept of chronic atrophic arthritis does not admit a known single specific etiological agent, nor likewise a specific cure. There are many factors concerned in the etiology of this disease, and it is a disease not only of the joints, but is constitutional in scope, manifesting itself in nearly every system of the body. The following diagram (table 2) schematically illustrates this.

This illustration is intended to show the complexity of etiological factors and the difficulty of a direct approach to therapy. It is possible, at a glance, to see the enormous number of combinations available with so many variables. The manifestations of infection are in a large measure determined by variations in other factors, a few of which are listed in the left and right hand columns. We do not know that infection always behaves in this manner, though there is considerable evidence to suggest it, but it serves as an illustration of the possibilities. When one considers this problem from the standpoint of therapy, it becomes exceedingly complicated

TABLE II



and illustrates well the fallacy of assuming that certain results in treatment are due to one specific therapeutic agent. It is because of the many sided nature of such a chronic disease that therapy, to be effective, must depend not upon one agent but upon every factor possible. Therapy then, of chronic atrophic arthritis, should concern itself first of all with the patient's general health and it is with this in mind that, after trying a long list of therapeutic measures, we have selected but a few that seem worthy of mention. These are tabulated in table 3.

TABLE III

General Therapeutic Measures	*Special*
Rest and Exercise	Removal of Foci
Heat and Massage	Transfusion
Prevention and Correction of Deformity	Vaccine
Diet	Climatic Therapy
Bowel Management	1—General—Residence
	2—Special—Heliotherapy

All of these patients with atrophic arthritis received the first five general measures, as well as general climatic therapy. In addition to these measures, approximately 100 patients had foci of infection removed, 70 were transfused, 100 were given vaccine, and 100 had only special climatic therapy in addition to general measures. Every attempt was made to establish an adequate control period on general measures, before beginning any one of the special types of management.

GENERAL MEASURES

Rest and Exercise. One of the first problems confronting the physician is determining the relative proportion of rest and exercise desirable for a given patient. In general, rest should be directly proportional to the acuteness, and inversely proportional to the imminence of ankylosis. Exercise should almost always be active and almost never passive. Motion should be limited to within the painless arc, but pushed to the limit with some assistance. All exercises should be done slowly and exactly, with a rest interval

before the next one is begun. We use under water exercises in much the same way as they are used at Warm Springs, Georgia, for paralytics. A very much wider range of joint motion can be secured without pain or muscle spasm than is otherwise possible. By varying the temperature of the water, any degree of sedative action or of stimulation can be secured. We are firmly convinced that the salvation of many patients with chronic arthritis depends upon regular and wisely directed exercise, for with atrophic arthritis in its more chronic phases, it is truly a case of use or lose.

Heat and Massage. The application of local heat to the joints is, in our opinion, utilized too much and is a factor in keeping an arthritis active that might otherwise subside. The greatest precaution should be exercised in utilizing heat, unless the stage of the disease is a very chronic one. Diathermy, as a method of heat in these atrophic demineralized joints, has in many instances precipitated exacerbations and has produced further demineralization. Massage, in the acute stages, should be avoided, and only with increasing chronicity should stimulating massage be used. Light massage can be used very early and is the best substitute if active motion is not possible. It is in other types of arthritis that heat and massage are indispensable. It should be noted that the "*a*" group tolerate heat and massage much better than the "*b*" group. Local heat to the joint ought not to be followed at once by exercise, as is generally done. Stripping, depletion massage, or rest should precede exercise as further damage will occur in exercising an engorged joint. Massage and active educational exercises provide three-fourths of the physiotherapy given in our Hospital. It should be pointed out that little special equipment is necessary for this work, but a trained personnel is essential.

Prevention and Correction of Deformity. In every case of atrophic arthritis, the possibility of residual deformity in any and all involved joints should be anticipated. The prevention of such deformities can be accomplished only at the price of eternal vigilance. Their correction requires infinite patience. Nearly all deformities in this unhappy disease occur in flexion. Particularly is this true of the spine, elbows, wrists, hips, and knees. Eighty per cent of all patients with chronic atrophic arthritis, entering our clinic, have a flexion deformity of one or more joints, which might have been prevented. In the acute stage the joints should be at rest at the normal angle of relaxation. Light splints, or light weight plaster of paris shells, are most useful in maintaining the ideal position of the joint. Weight bearing upon a bent knee is not only painful, but increases the deformity. Flexion deformity of the knee can usually be prevented by the simple use of a posterior splint, and a knee already so deformed can in most instances be straightened by the application of a series of plaster of paris posterior shells. Painful pressure, wedge casts, and calipers are not usually necessary, as relaxation and protection will usually bring the knee to a normal weight bearing angle. Corrective exercises accompanied by proper rest are necessary. Group muscle exercises, particularly of the extensors, can be done

without joint motion and should be carried out routinely. Active joint motion, without weight bearing, can be begun very early and will maintain muscle tone and joint mobility without injury.

The feet and the proper fitting of shoes are of first importance, as the patient's ability to walk depends upon his feet. We are convinced that many patients, who might otherwise be reasonably free from discomfort, continue to experience the greatest difficulity in walking, because of improper shoes. It should be emphasized again that prevention of most deformities is not difficult, but correction is most painful and trying.

Diet. Diet does play a very real rôle in the treatment of these patients. Dr. Pemberton of Philadelphia has said many times all that can be said on this subject, and with him we are in hearty agreement. A diet low in concentrated carbohydrates and high in vitamins is essential, where the patient's state of nutrition will tolerate it. A rigid dietary restriction we believe to be much more efficacious in the "*a*" group of atrophic arthritis than in the "*b*" group. Where the patient is poorly nourished and emaciated, we discard most dietary restrictions until a better state of nutrition is secured.

Bowel Management. The majority of patients with atrophic arthritis have a history of gastrointestinal disturbances and, in most instances, complain of constipation. The colon is often tortuous, the sigmoid redundant, and there are areas of spasm in an otherwise very atonic bowel. Routine proctoscopic and sigmoidoscopic examinations, with cultures from the mucosa, have been made in more than 200 of these patients. The majority show some deviation from normal in the mucous membranes. Proctoscopic examinations have been repeated after a series of colonic irrigations, oil enemas, acidophilus implantations, etc., without noticing, except in a few instances, any demonstrable change in the mucosa. There is no doubt but that in our experience adequate bowel elimination has contributed to the patient's comfort and that joint exacerbations do occur in a number of patients when gastrointestinal disturbances occur. Adequate intake of vitamins is helpful, but we have been unable to demonstrate with any regularity the remarkable changes in the colon on this routine reported by other investigators. The stool reaction of these patients is nearly always alkaline. Normal stools are neutral or slightly acid. The colon bacillus grown at the pH of a normal stool is non-pathogenic for animals. The same organisms grown in an alkaline medium become highly virulent for animals. We have had considerable success in a small group of patients by maintaining a slightly acid reaction of the stool. Further work is being done in this field. Bowel regulation is ordinarily maintained without cathartics by the use of a good mineral oil, or mineral oil and agar by mouth. A small retention oil enema may be used at night if necessary. It is difficult properly to evaluate therapy, but a sufficient number of patients have been seen who present demonstrable changes in the joints with faulty bowel management to convince us that it does play a rôle in some patients.

Special Measures

Three hundred and seventy patients with chronic atrophic arthritis, after receiving the above general measures during a control period, were divided into four comparable groups. Each group was then treated by one of the four special therapeutic measures.

Removal of Foci of Infection. (One hundred patients.) The removal of foci of infection in the "*a*" group of atrophic arthritis (table 1), has been very disappointing. No single patient that we have seen in this group has unquestionably benefited by the removal of a focus. Quite the reverse is true, however, in the "*b*" group, where removal of foci early will many times abruptly halt the disease. Here again, however, the possibility of benefit by removal of foci decreases with the duration of the disease. This is indeed so striking that very rarely are we hopeful of a beneficial result from removing a focus, when the disease has existed as a full blown atrophic arthritis for five years or more. It is worthy of emphasis that in nearly all patients of the "*a*" group and most of the "*b*" group, who are in the very chronic stage, the removal of a focus is apt to be not only not beneficial, but to be followed many times by acute exacerbations. We have in the records of these patients many such instances when removal of foci was followed by an unmistakable increase in the severity of the disease. In the early stages of the "*b*" group, where striking benefit is most likely to occur, a real hazard still exists in the removal of foci. We not infrequently precede the removal of a tooth or tonsils in an ideal case with a transfusion and take particular care not to remove the focus during, or near, an acute phase of the disease. Patients in the early stages of infectious arthritis should be treated for a reasonable time by all other measures possible, in an attempt to arrest the disease, and then under the most suitable conditions removal of foci of infection should be accomplished. If foci are removed in the more chronic cases, it should be done because of general considerations and not with the hope of cure.

Transfusions. (Seventy patients.) Patients in the subacute and early chronic phases of infectious arthritis, with or without anemia, respond well and in not a few instances dramatically to a series of small blood transfusions. In the patient who responds well, the temperature drops to normal, the pulse rate is slowed, joint effusions disappear, and the patient goes on to gradual recovery. Transfusion, in our opinion, can be used with advantage routinely, in suitable cases, as it is one other aid that hastens recovery and prevents the disease from progressing to its more chronic aspects. Transfusion has been of little help in the very chronic afebrile patients, with far advanced bone changes.

Vaccine. (One hundred patients.) So voluminous has been the literature recently regarding the use of vaccine, and so much has been claimed for the many different kinds of vaccine, that we have attempted to carry out some controlled experiments on its use. We have given vaccines to com-

parable groups of patients, using a wide variety of antigens. Skin tests were made with autogenous cultures, as well as with stock arthritis-producing streptococci. Several strains of streptococci from other investigators were also used. Specific agglutinations with the patient's serum were done against these organisms. Stock or autogenous vaccine was given intravenously or subcutaneously in small doses and in large enough doses to produce slight reaction. Some patients were given only skin reacting organisms, while others were given only nonreacting ones. Still others were treated only with those organisms showing a positive agglutination. In general, almost every combination of antigen and method of administration has been tried on nearly every degree of atrophic arthritis. The results have been checked by repeating the skin and agglutination tests at intervals, as well as by clinical criteria.

Undoubted clinical improvement, not easily accounted for otherwise, occurred only occasionally. No single one of the above groups did well enough to show clearly superiority of results over other groups not receiving vaccine. Our best results with vaccines have occurred where an autogenous organism, which showed a strong positive skin sensitivity test, was used in small desensitizing doses intravenously. We have had a few dramatic results in this group of patients. The use of vaccine is not without hazard, as we see daily in the clinic patients who have had very unhappy reactions from its use. We have had an occasional unfortunate result in our own practice, in spite of exercising the greatest care. No patient offers a more difficult therapeutic problem than one who has had unfortunate vaccine reactions or one who has been highly sensitized by its use. Shock therapy, either by vaccine or nonspecific protein, is a hazardous procedure in patients with early or subacute forms of atrophic arthritis.

It is time to call a halt on the promiscuous injection of vaccines. There are investigators who report a large percentage of cures by giving millions of organisms intravenously. Others, equally sincere, report similar results when the equivalent of less than one organism is used. There are ardent advocates of subcutaneous and of the intravenous method of inoculation. Stock vaccines are championed by some and decried by others. Agglutination, complement fixation and skin reactability have all been defined as guides to diagnosis and therapy. Constitutional reactions are believed to be desirable or harmful, depending upon the investigator. When the patient improves, the agglutination titer is thought to go very high or very low, depending upon the laboratory in which it is done. What then is the explanation for the many reports of cures secured by such diverse methods? There are two factors that may be responsible. The natural course of atrophic arthritis consists of cycles of exacerbations and remissions. Out of this group of patients 60 per cent recovered or were remarkably improved, from the first attack of the disease. Whatever form of therapy was being used at the time was naturally credited with the cure. We wish to emphasize again that particularly in the early stages of atrophic arthritis the

tendency is to remission, and that in this respect the course of this form of arthritis is not unlike that of pernicious anemia. Unfortunately, when the patient's arthritis recurs, he often seeks other medical advice, so that little is learned concerning the progress of the disease over a number of years. Successive exacerbations become more chronic in nature and less apt to be followed by a spontaneous remission. A second possible explanation is that the term " atrophic arthritis " is used very loosely and in many instances is incorrectly applied to patients with everything from pes planus to wry neck. It is also necessary to point out again that the state of the patient, classified by the investigator as " improved," is unsuitable for statistical data.

Clinical experiments are still in progress, but in our present state of knowledge we feel that vaccine has a limited value, is not a panacea, and should only be used as an adjunct in treatment and then only where complete facilities are available for following the patient and under experienced medical direction.

Climatic Therapy. (One hundred patients.) There are many difficulties encountered when one attempts to prove the specific effect of any therapeutic aid in chronic diseases, but this is especially true where climate is concerned. The resort to climatic therapy usually involves a change of location, which may provide a variation in daily routine, increased rest, freedom from annoying business worries, escape from unhappy domestic situations, and a psychic stimulation provided by a suggested new cure. All of these must be weighed and considered when discussing results. There are often in addition certain changes in diet, medication, bowel management, and activity, associated with the change of physicians. These many possible variables emphasize the necessity for the greatest conservatism when reporting results from a change in climate. There are, however, a number of significant observations that appear even under the strictest scrutiny to support the widespread belief that climate may be a predominant factor in the etiology and in the treatment of chronic arthritis. Several of these observations will be discussed briefly.

Some months ago, it occurred to this writer that climate might best be studied if comparable groups of non-nomadic people living under different climatic conditions could be investigated. Arrangements were made for a survey on a tribe of Indians who have lived continuously on the Tucson desert for several hundred years. The incidence of atrophic arthritis in these Indians could then be compared with that of Indians in other climates. This survey is still in progress but no cases of atrophic arthritis have been seen yet among these 5000 Indians. So far we have not examined the Indians in Montana, Wyoming, or Dakota, but have reports that arthritis, acute and chronic, ranks high as a cause of disability among them. This low incidence in the desert Indians is more startling when one finds them living largely on beans and corn, and carrying about abscessed teeth and many other foci of infection. No striking difference is found in the diet or method of living in the two groups of Indians. There seems to be only one variable factor,—the climate.

One hundred and twenty-two physicians of this locality were written to, or interviewed, regarding the incidence of atrophic arthritis in native residents of this vicinity. There were but two cases reported. We have seen only one case of atrophic chronic arthritis in a resident in the course of this last 1000 patients.

It is also of interest in this connection to note that rheumatic fever is very rare in this locality and to report that of 52 patients referred to us in the past three years, with recurrent rheumatic fever, no patient has had a frank recrudescence during his stay here. Eight were in an acutely active phase on arrival, which subsided within a few weeks. One died in an acute phase shortly after arrival. It is of course recognized that sufficient activity may be present to produce rheumatic lesions but remain undetected clinically. We have used the clinical course, temperature range, electrocardiogram, and sedimentation time of erythrocytes as guides to activity. Coburn, in his recent book "The Factor of Infection in the Rheumatic State," makes out a very strong case for the beneficial effects of climate in rheumatic fever. His results in transferring patients with rheumatic fever to Puerto Rico are entirely in accord with our experience when such patients are brought to southern Arizona.

One hundred patients with atrophic arthritis were selected for this study on climatic therapy. They were selected without reference to severity of disease, but on the basis of having been treated as nearly as possible by general and special climatic modalities alone. No patient was included who had foci of infection removed, or who was treated with various specific medications or vaccines. Patients who had special diets and exercises could not be excluded, and there were without doubt many other uncontrolled factors. It is only fair to state that a large majority of our patients come to us in a very chronic stage of the disease and may be termed "last resorters." The results in this group of patients have been most gratifying. The majority have made definite and sustained improvement. A few made dramatic recoveries, and a few were unable to accomplish any distinct gain at all. As has been stated before, the number of variable factors is so great that no proof can be offered as to the specific rôle played by climate in this group of patients. It is equally difficult to evaluate any other type of therapy. We were, however, convinced by comparing their previous experiences with various types of treatment, that climate played a very important rôle in the improvement secured.

The total effect of climate is a composite of such things as humidity, temperature range, altitude, barometric pressure, wind velocity, rainfall, concentration of ultra-violet, total sun energy, ionization of air, type and character of exposure to sun, etc. We are now attempting to determine which are the significant factors. Graphic records are being kept on all of the above data and these are being studied in conjunction with the patient's signs and symptomatology. A warm, dry climate and a minimal barometric variation at present seem essential. Various forms of heliotherapy constitute the major portion of specific climatic therapy.

It is not the intention of this writer to suggest that climate is a panacea for all chronic arthritis. On the contrary, we feel that no possible additional therapeutic aid should be neglected. However, there is sufficient evidence to show that carefully supervised climatic therapy is a potent factor and a valuable adjunct in the treatment of atrophic arthritis. Further studies are being made to determine what the essential factors in climate are, and to clarify their modes of action.

Discussion

A single easy successful treatment for chronic atrophic arthritis is not yet available. It is not the intention of this writer to sound a pessimistic note, for we have reason to be most optimistic in the results secured by adequate treatment. We do, however, believe that it is time for the medical profession, as well as the victims of this unhappy disease, to recognize that there is no easy way. Every patient with chronic arthritis becomes an individual problem, and requires, in addition to full medical care, the ideal patient-physician relationship before there can be any hope of success. In any chronic illness the psyche must be considered, but the writer knows of no condition in which it plays a more important rôle than in chronic atrophic arthritis. The ideal treatment of this disease will require of the physician an enormous expenditure of nervous energy and the patience of Job, for there must be careful and methodical consideration of each individual problem. The management is made more difficult because of the mental depression so common to patients with this disease. They are often migratory, seeking always some new cure. The patients of our group had consulted an average of three different physicians or clinics before entering here. A tremendous advance in the therapy of this disease can occur if physicians will only stop treating these patients half-heartedly by every new or easy method recommended, and will tell them honestly what the problem of adequate treatment includes. There is little to choose between the physician who treats with an ointment the lump in a woman's breast, and the one who does not recognize or treat wisely the early manifestations of atrophic arthritis. Cancer, fortunately, kills its victims, but unchecked chronic arthritis leaves its victims a lifetime of crippling deformity and pain.

Summary

1. One thousand patients with the various types of chronic arthritis were classified and studied. This paper is limited to a consideration of therapy in atrophic arthritis, of which there were more than 300 in this series.

2. After trying a very great number of therapeutic procedures, nearly all were discarded. The worthwhile methods are tabulated and discussed.

3. All patients were treated by general measures such as rest, exercise, heat, massage, prevention and correction of deformity, diet and bowel management. Indications and contraindications for these methods are enumerated.

4. Groups of patients after being treated by general measures for a control period, were given special types of therapy and over a period of several months or years, comparisons of results were made. Removal of foci of infection, transfusion, vaccine, and special climatic therapy were the special methods used on four comparable groups. The most striking result of this experiment was to prove the nonspecificity of any therapeutic agent tried.

5. Removal of foci is of value in the subacute or early chronic stage of the infectious "*b*" group. It has been found of little help in the "*a*" group and in the very chronic stage of the "*b*" group. Removal of foci is often disastrous unless adequate precautions are taken.

6. Blood transfusions were very helpful in a group of subacute and early chronic cases, but were of little value in the very chronic afebrile cases with advanced bone and joint changes.

7. Vaccine has a definite but limited place in the therapy of atrophic arthritis. No favorable results were secured from its use in the "*a*" type. In the "*b*" group, skin reacting autogenous organisms in minute desensitizing doses, intravenously, gave the most favorable results. It is believed that much harm is done by the indiscriminate injection of vaccines. The present practice of distributing stock vaccines to the general profession for the treatment of chronic arthritis is deplored.

8. Climate is believed to be a potent factor and a valuable adjunct in the treatment of atrophic arthritis. The following evidence is presented:

(*a*). There is a low incidence of atrophic arthritis in local Indians, as compared with similar tribes elsewhere.

(*b*). There is a low incidence of atrophic arthritis in native residents in the vicinity of the Tucson desert.

(*c*). In a group of 100 patients with atrophic arthritis, gratifying results were obtained in a large proportion without resort to any specific therapy other than the general measures described and climatic treatment. It is our belief that, inasmuch as most of these patients had tried nearly every other known remedy, the satisfactory results can in a large measure be ascribed to carefully supervised climatic therapy.

9. A plea is made to physicians to stop treating these patients with every new cure suggested, to recognize and treat wisely the early manifestations, and, above all, honestly to explain to the patient the numerous factors necessary to giving him adequate care.

THE INDICATIONS FOR COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS*

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The literature of the past five years on the treatment of pulmonary tuberculosis, impresses one with the nearly universal enthusiasm for collapse therapy. Characteristic of the mechanical age in which we now live, the treatment of tuberculosis is rapidly being placed on a mechanical basis, in much the same way as the "go out West and rough it" formula was advocated by many four decades ago. That tuberculosis is primarily a constitutional disease with local manifestations is overlooked by many enthusiasts. Extravagant statistics, frequently compiled prematurely, attempt to prove the efficacy of favored surgical procedures, and premises have recently been advanced [1] to justify collapse therapy in every case of unilateral pulmonary tuberculosis. Such waves of enthusiasm for a new form of treatment are familiar phenomena in medical history, as is the aftermath of disillusionment, endless suffering and protracted invalidism. A conservative discussion, therefore, of the indications for the various types of collapse therapy, with the thought in mind that they are only aids and not specifics, is deemed advisable.

The Curability of Pulmonary Tuberculosis by Rest and Hygienic Living

For clinical purposes, two types of pulmonary lesions need be considered; first, the acute or exudative type, characterized by a rapid onset with either limited pneumonic consolidation or scattered fluffy parenchymal deposits through one or both lungs; second, the proliferative type, insidious in onset, chronic from the start, slow in progression and with a pronounced tendency towards fibrous tissue formation. In favorable cases, healing occurs by resolution, that is by absorption of the exudate, or by fibrosis which encapsulates the disease and ultimately replaces it by scar tissue. If the disease is recognized before softening and excavation have occurred, regardless of the extent of the process, a large number of patients will recover under the old formula of rest, fresh air and good food. Physiologic rest is the keynote of treatment, aided by such additional measures as the education of the patient to suppress the cough, postural rest and the use of shot bags.[2] It should be continued for as long a time as there is encouraging evidence of improvement. Striking as have been the results from pneumothorax and surgical measures when the rest regime has failed, the results from the latter

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have in numerous instances been even more remarkable and more enduring. It would be a calamity if physicians and specialists, in their desire for short-cuts to success for their patients, forgot the inestimable value of rest treatment and its underlying principles. Upon these principles, after all, are based all the modern procedures of collapse therapy.

For a reasonably accurate determination of a patient's progress when on a conservative regime of treatment, clinical observation alone is not always a reliable guide. Progressive caseation-necrosis with cavity formation is not incompatible with a normal pulse and temperature. There need not necessarily be even an increase in cough and sputum or a loss in weight. Serial roentgenograms taken at intervals of three or four months and more frequent fluoroscopic observations are therefore of paramount importance. Of nearly equal value are hematologic studies, notably the erythrocyte sedimentation test and the determination of the leukocyte-lymphocyte ratio. A persistently high sedimentation rate and a leukocytosis with a high polynuclear count in the absence of non-tuberculous inflammatory conditions, call for a painstaking search for tuberculous involvement of other organs. If the explanation is not found in the presence of such a complication the suspicion should be aroused that the disease in the lungs is not pursuing a favorable course despite apparent general improvement. If the indications furnished by these laboratory methods when properly coördinated with the clinical manifestations are followed, the average patient who comes under medical care before cavitation has formed has more than an even chance to recover under a conservative plan of treatment.

The High Incidence of Advanced Cases

It is, however, a sad fact that over 75 per cent of patients are already in the moderately advanced or far advanced stages of the disease, frequently with extensive cavitation, before they apply for treatment to the qualified physician or institution. Mistakes in diagnosis and haphazard treatment, or neglect, fear or ignorance on the part of the patient account for this condition. The practice of many county and state tuberculosis sanatoria of not housing patients for more than six or nine months, and the failure of social agencies properly to bridge the gap between sanatorium life and the competitive world are also important factors, and must annually be responsible for thousands of advanced cases which can no longer be cured by natural methods. These are the patients for whom artificial aid is indicated. Cavities exceeding the size of five centimeters in diameter rarely become obliterated from rest alone. Untreated, a number of them may retain for a time a certain degree of physical efficiency, but the majority are chronic invalids and ultimately die in from four to six years.

The main problem, obviously, is the advanced case. The National Jewish Hospital at Denver recruits patients from every State in the Union and Canada. The average duration of the pulmonary disease in these cases

is five years, and 75 per cent of them have already had one or more residences of varying length in hospitals or sanatoria. Over 70 per cent of these patients present on admission evidence of far advanced fibro-cavernous pulmonary tuberculosis. In brief, our material is composed chiefly of tuberculous derelicts who have gone through the melée and have scored once or several times apparent victories but have failed to attain the goal. A critical analysis of the history and clinical course of each individual case discloses an appallingly large incidence of relapses, due often, it is true, to the adverse economic conditions which are the lot of the average consumptive, but often also attributable to ineffective treatment. The assertion [3] that nearly every far advanced case has at one time in the course of his disease been suitable for some form of collapse therapy is well borne out by a study of the material at our disposal. It is because so many cases present the tragic story of lost opportunities, often through no fault of their own, that the question of the advisability of collapse therapy has come to be our first consideration following the initial examination of a tuberculous patient. The fact that we have been successful in securing marked amelioration of symptoms and many cures in a considerable number of apparently hopeless cases, has enabled us to offer a more favorable prognosis to those who only a decade ago were considered beyond medical aid.

Maximum Time-Limit for Conservative Treatment

It is realized that individualization is one of the most important requisites to intelligent treatment. Not until a specific remedy is discovered will there be a therapeutic measure applicable alike to all patients with tuberculosis. Nevertheless, the following axioms may be safely formulated: A patient between the ages of 15 and 50, not in the terminal stages of the disease and free from grave tuberculous or non-tuberculous complications, who fails to improve in six months under a properly conducted rest regime should be considered as a possibly suitable subject for collapse therapy. Serious symptoms, such as recurring hemoptyses, or physical and roentgen evidence of beginning cavitation, justify resorting to collapse measures at an earlier date. If the disease is of one year's duration or longer, and rest treatment has already been tried elsewhere, one or two months of observation should suffice to determine the type of new treatment indicated. Procrastination is fraught with dangerous possibilities [3] and physicians have more frequently regretted [4] not having instituted pneumothorax than having started it too early.

Principal Types of Collapse

The three methods of collapsing a diseased lung, in the order of their importance and range of applicability, are (1) artificial pneumothorax; (2) phrenicectomy; (3) thoracoplasty. The aim of each method is identical in every respect, namely, to relax or collapse the affected lung sufficiently to promote a maximum of healing by either resolution or fibrosis, and to

prevent metastatic spread of disease and hemoptysis by obliterating discharging cavities. However, owing to the fact that each method has its distinct advantages, disadvantages and limitations, their respective indications must be considered separately.

Indications for Artificial Pneumothorax

A useful rule by which to be guided in choosing a type of collapse therapy to fit the individual case is the simplicity, effectiveness and flexibility of the procedure. Pneumothorax excels in these advantages and should, therefore, be tried first before other methods are undertaken. The technic of administering filtered air into the pleural cavity is easy, although considerable skill and judgment are necessary in the general management of these cases, and particularly in treating such complications as effusions, empyema, adhesions and, rarely, air embolism. In the absence of pleural adhesions, a better collapse of the lung can be secured by artificial pneumothorax than by any other method. There is very little reaction following the initial treatment, and practically no untoward effect in uncomplicated cases after subsequent air refills. The indications may conveniently be divided into *absolute* and *provisional*. The *absolute* indications are:

1. Extensive unilateral exudative or fibro-caseous pulmonary tuberculosis, with or without recognizable cavitation by physical signs or the roentgen film. Bacillary sputum of 15 cubic centimeters or more in twenty-four hours usually indicates cavitation. The more definite and the more extensive the cavitation, the more cogent is the indication.

2. Chronic unilateral fibro-ulcerative tuberculosis, with cavitation ranging in size from three to five centimeters in diameter, even if constitutional symptoms are absent. The only effective insurance against a bronchogenic spread of the disease to the uninvolved lung is closure and final obliteration of cavities.

3. Profuse hemorrhage or recurrence of pulmonary bleeding when the source of the latter is ascertained with a reasonable degree of accuracy. While hemoptysis, as a rule, stops of its own accord, the institution of pneumothorax is justified when hemostasis cannot be secured by medicinal measures, or when the bleeding recurs and constitutes a danger of either exsanguination, spread of the disease or aspiration bronchopneumonia. Too much consideration should not be paid to the condition of the contralateral lung even if extensively diseased. Without pneumothorax the danger to life is decidedly greater.

4. Acute unilateral pneumonic tuberculosis. If the constitutional symptoms are marked and the toxemia is profound, excavation may occur in as short a period as one week. This can be prevented by the early collapse of the lung. On the other hand, if the symptoms are mild, watchful waiting is permissible, provided frequent roentgenoscopic and roentgenographic examinations constitute an essential part of the clinical observation.

The *provisional* indications are:

1. Bilateral disease with unilateral single or multiple cavitation. The frequency with which most pneumothorax operators have seen marked clearance of the lesion in the better lung following the successful collapse and closure of cavities in the more diseased lung warrants this recommendation for selected patients whose general condition is still good and who present other evidence of some degree of natural immunity. The contralateral disease must not be of the acute pneumonic or exudative type; but scattered proliferation with small patches of exudation frequently undergo resolution after the subsidence of the constitutional symptoms and the reduction in cough and sputum which so often follow a successful pneumothorax. It is fallacious to speak of an extra physiologic burden thrust upon the better lung in connection with pneumothorax therapy. In a properly managed pneumothorax uncomplicated by pleural adhesions, only the major diseased portion of the lung, as a rule, need be collapsed, while the lower, less involved area is only relaxed and is partially functioning. Furthermore, where one lung is extensively involved, the chief burden of respiration is already carried on by the contralateral lung. Finally, the reduction of toxemia and the subsidence of the traumatizing cough materially aid the better lung to function with a minimum of embarrassment.

2. Bilateral disease with extensive cavitation in one lung and small, thin-walled upper lobe cavitation in the other lung. Untreated, the majority of patients with such type of involvement are doomed. Rest alone rarely suffices. The cautious collapse of the more diseased lung frequently aids not alone in improving the condition of the contralateral lung, but in closing such early limited cavitations as it contains. This obtains especially in cases where the mediastinum is flexible, as the slight or moderate displacement of the mediastinum toward the less affected lung causes a certain degree of splinting and relaxation of that lung. This compression of the less affected lung constitutes an added important contributing factor to the healing process.

3. Bilateral pneumothorax. When a case such as described under the last heading fails to improve after a satisfactory collapse has been established, and there is reason to believe that the symptoms are now due to unchecked activity or progression of the disease in the contralateral lung, simultaneous bilateral pneumothorax is justified. Experience has shown that young individuals between the ages of 15 and 30, whose disease is of relatively short duration, and in whom there is no evidence of myocardial impairment, tolerate bilateral pneumothorax very well. It is, in selected instances, as compatible with a useful and efficient life as unilateral pneumothorax. However, this is true only of those patients in whom the physician is fortunate enough to obtain a selective collapse of the upper lobes, where the disease is usually localized, and only a slight relaxation of the lower lobes which will not interfere with their proper physiological function.

4. Chronic fibro-cavernous disease of one lung and more recent acute

disease in the other lung. If, after a regimen of rest for two or three months without improvement, physical examination and the roentgen film disclose a stationary condition of the older excavated lesion but progression and early cavitation in the better lung, it is good judgment to collapse the latter with the thought in mind that after a year or two of such treatment the lung may be safely reëxpanded and attention then paid to the problem of the primary diseased lung. Such a procedure is logical and has proved useful in preventing the occurrence of extensive bilateral cavitation for which there is admittedly no remedy.

5. Alternating pneumothorax. Acute contralateral disease during pneumothorax therapy is a grave complication and is responsible for a high mortality.[5] A collapse of the newly involved lung is permissible if the patient is otherwise suitable for such treatment. On the other hand, where the first pneumothorax has already been maintained for two years or longer with cavitation apparently closed, it is much safer to allow that lung to reëxpand either before collapsing the other lung or as soon as the collapse is initiated. Alternating pneumothorax [6] has proved of much value in patients past the age of 30 and in younger individuals in whom simultaneous collapse is contraindicated because of evidence of myocardial insufficiency.

Mechanical and Physiological Factors Responsible for Beneficial Results from Pneumothorax

The interposition of several hundred cubic centimeters of air between the parietal and visceral pleura at once reduces the effectiveness of an adhesive force, the normally existing negative intrapleural pressure, which greatly militates against adequate rest for a diseased lung. At the same time, this air splint relaxes the elastic tissue of the lung which is greatly stretched during each inspiration. The elimination or reduction of the negative intrathoracic pressure and the overcoming of the elastic recoil of the lung are the most important and the most effective mechanical factors in securing the additional much needed rest for the involved lung. Following several air refills, the lung is more immobilized and its respiratory activity reduced to a minimum. As the lung becomes reduced in volume, the secretions diminish as they are more easily eliminated, and the cavitation gradually closes. The almost dramatic suddenness with which improvement sets in is said to be due to a decrease in toxic absorption from the diseased area as a result of lymph stasis and diminished blood supply. The continuous increase in fibrous tissue during the time the lung is collapsed aids greatly in the encapsulation and healing of scattered diseased areas.

End-Results of Pneumothorax

Our experience coincides with that of Amberson,[7] Peters,[8] Packard [9] and others. An effective pneumothorax, properly managed and maintained for three years or for a minimum of one year from the time the sputum becomes

negative for tubercle bacilli, will cause an arrest of the disease in from 75 to 85 per cent of patients and restore them to normal working ability. In the average case, one year of hospitalization or rest at home is sufficient to enable the patient to return to a useful life provided the gas refills are continued at stated intervals. Three times as many patients are known to be alive two to fourteen years after treatment by pneumothorax as have survived from those in whom pneumothorax was attempted without success on account of failure to find a pleural space. Three times as many pneumothorax patients are leading a normal existence.[8]

Nevertheless, it is important to point out the large incidence of pleural complications of pneumothorax therapy. As we have pointed out elsewhere [3] these complications are in direct proportion to the extent and duration of the pulmonary disease. In a series of 176 patients in whom we induced pneumothorax during the past five years, 65 per cent had serous effusions, 18.7 per cent purulent effusions, and 5 per cent died ultimately from empyema. This indicates that pneumothorax, while in itself a simple procedure, has an ultimate mortality of from 3 to 5 per cent, assuming that in early cases the occurrence of empyema is less frequent. Based upon these figures, an eloquent plea could be made for more conservatism. However, long experience has shown that the majority of those patients in whom pneumothorax or other collapse measures are indicated and for some reasons are not performed die after varying periods of invalidism and intense suffering. The present day physician who does not avail himself of modern surgical treatment in properly indicated cases is unjust to his profession and harmful to his patients.

Impediments to Good Results

The first and most important hindrance is pleural symphysis. In 26.3 per cent of our patients upon whom pneumothorax was attempted, no space was found after several explorations in different localities. When a space is found and string-like adhesions are present, they can be stretched sufficiently in the majority of patients by the cautious continuation of gas refills to eventually effect a good collapse without resorting to intrapleural pneumolysis.[10] According to a recent report,[11] Unverricht himself is doing now one operation for the division of adhesions where he did ten five years ago. The dangers of hemorrhage, pleural effusion, or perforation of a cavity with the subsequent development of empyema, must always be considered in connection with intrapleural pneumolysis, notwithstanding the successful results reported by some authors.[12, 13] In our experience, clear cut indications for pneumolysis are found in not more than 3 per cent of pneumothorax patients. By utilizing phrenicectomy to relax these adhesions, that figure can be greatly reduced.

The thick-walled cavity is another cause for pneumothorax failure. The lung in such instance may be seen well collapsed, but the cavity remains

patent because of failure of the thick wall surrounding it to yield to external pressure. String adhesions are frequently seen radiating from such cavities toward the chest wall, but their severance with the cautery fails to close the cavities, for the problem is not so much the adhesions as the thick wall itself.

More of an obstacle than string adhesions or even thick-walled cavities are broad-band adhesions which completely prevent a collapse of the lung above the third or second rib, i.e. at a level where the lesions are nearly always associated with cavitation. Here the object of the pneumothorax is entirely defeated, unless there is considerable pulmonary involvement below the level of the adhesions, in which event the patient may obtain for a time marked symptomatic relief. However, since the main objective is the closure of cavities, it has become our practice not to continue pneumothorax with uncollapsed cavities for more than one year, even if satisfactory palliative results have been obtained, without urging the patient to submit to other surgical procedures. The dangers of an uncollapsed cavity, besides hemorrhage or metastasis to the better lung, are not sufficiently appreciated by otherwise experienced pneumothorax operators. Most of our fatal empyema cases with bronchial fistulae that have come to autopsy have shown tears in a cavity wall which probably would not have occurred if pneumothorax had not been continued too long. It has long been our contention that a cushion of air interposed between the chest wall and the lung is not nearly as good a support to a diseased lung as the chest wall itself. This is the most likely reason for the greater frequency of spontaneous pneumothorax during the course of induced pneumothorax,[14] and it is not improbable that many pleural effusions are caused by small-sized unrecognized pulmonary perforations. It is because of these dangers and the failure to achieve the main objective that patients with partial and incomplete pulmonary collapse have to be submitted to more radical surgical treatment.

Phrenicectomy

As statistics accumulate and the longer phrenicectomized patients are observed, it becomes clear that the value of phrenicectomy has been much over-rated. In our series[15] of 183 patients, an arrest of the disease from this procedure alone was obtained in only 12 or 6.6 per cent. It is also of importance to note that of the seven patients who had unilateral lesions either without, or with doubtful cavitation, only four showed an arrest of the disease when examined at the end of from one to three years. It is difficult to reconcile our results with the teaching of those[16] who advocate phrenicectomy in preference to pneumothorax for all patients with unilateral lesions, without even affording them the benefit of a six months period of conservative treatment. It is generally conceded that pneumothorax carries with it greater dangers and that it is a much more tedious and protracted treatment than phrenicectomy, but the comparative results of the two methods are evidently a matter of individual experience. Statistics are decidedly mis-

leading unless accompanied by a detailed description of the material studied As a means of closing well formed apical cavities, phrenicectomy has definite and marked limitations, although occasionally a surprisingly good result is obtained. Nevertheless, phrenicectomy has a wide range of usefulness. Its value is notable in the following conditions in the order named:

1. As a palliative measure to control excessive cough, especially of the emetic variety, and copious tenacious expectoration in cases which present bilateral lesions with only limited cavitation in the better lung. In from 40 to 50 per cent of patients, the decrease in cough and sputum, the greater ease of expectoration, and the general improvement are quite marked and constant effects.

2. As a curative measure for chronic, unilateral, lower lobe, tuberculous or non-tuberculous lesions. The first simple sectioning of the phrenic nerve by Stuertz [17] was undertaken to meet such an indication; and for a time the operation was applicable only to lower lobe lesions. It is ineffective in lower lobe pneumonic phthisis and in bronchiectasis of long standing, and often aggravates these conditions.

3. To control profuse or recurring hemoptysis when pneumothorax cannot be induced.

4. To supplement pneumothorax by relaxing adhesions which prevent an effective collapse.

5. As a substitute for pneumothorax, when a free pleural space is not available, in cases of predominantly unilateral lesions of the subacute or chronic variety. In acute pneumonic tuberculosis it seems of little or no value.

6. In tuberculous empyema with or without bronchial fistula when thoracoplasty is contemplated. Occasionally, the latter is obviated following an ascent of the diaphragm with a consequent decrease in the size of the empyema pocket, and sometimes there also occurs a closure of the fistula.

7. As a measure preliminary to thoracoplasty, not so much to test the efficiency of the contralateral lung, as to improve the general condition of the patient and to make him a safer operative risk. However, where there is a giant upper lobe cavity and the lower half of the lung shows little or no involvement, a high ascent of the diaphragm sometimes causes stagnation of secretions in the cavity, and the latter increases in size.

To the skillful surgeon, a phrenicectomy is a minor operation. It is done under local anesthesia and usually takes not more than fifteen minutes for its completion. The patient's balance, no matter how delicate, is, therefore, rarely disturbed from the operation per se. While we [15] have had no direct operative mortality, a postoperative mortality, that is, death within one to two months after the operation, has been experienced in 2.7 per cent of our series, in contrast with 1.2 per cent reported by Berry.[18] This difference is due principally to insufficient caution employed by us in the selection of patients, some of whom were virtually terminal cases. It is a decided error to submit a patient to an operative procedure, even if it be of a minor char-

acter, on the basis that it is his only chance or that he has nothing to lose. If such a patient fails to obtain the desired result, or rapidly becomes worse and dies shortly after the operation, the latter gains local disfavor and other patients ideally suited for such an operation are reluctant to accept it.

Thoracoplasty

Since pneumothorax is available to only 15 per cent of patients as we see them, notwithstanding the wide range of indications, and since phrenicectomy is a curative measure in the same type of patients to the extent of only 6.6 per cent, it would seem that thoracoplasty should have a large field of applicability. Actually, this is not the case. Only 4.6 per cent of those patients treated unsuccessfully by pneumothorax were found by us suitable for thoracoplasty. Theoretically, the patient with a unilateral exudative lesion in whom pneumothorax cannot be induced should be ideally suited for thoracoplasty, but experience has taught otherwise. An operation of this type when the patient is in the stage of defense often leads to disastrous results. It is only when the acute stage with high fever, rapid pulse and other toxic manifestations has passed, and the patient is still not making satisfactory progress, that thoracoplasty may be undertaken.

The compromises which may be made with the contralateral lung in pneumothorax practice are absolutely forbidden in thoracoplasty. The trauma which ensues to the patient from the latter procedure may cause a reactivation of latent foci in the contralateral lung. It is, therefore, a good rule to defer thoracoplasty for at least a year from the time when the better lung last showed clinically or roentgenographically an active focus of disease. Although a report has recently been made [19] on the feasibility of bilateral upper stage thoracoplasty, it is doubtful whether such a radical measure will gain popular favor, for the reason that resection of the upper five ribs alone without pneumolysis rarely obliterates a thick-walled cavity, and also because there is forever the danger of a reactivation or spread of the disease in the untreated lung by the time the patient has sufficiently convalesced from the first operation. Not until a simpler surgical technic is elaborated will it be safe to deviate from the accepted conservative indications, especially with regard to the qualifications of the better lung.

Salient Points to Be Considered in the Selection of Patients for Thoracoplasty

1. *Resistance.* This implies a careful review of the patient's previous clinical course, the severity and frequency of relapses, how readily he responded to rest treatment, and such other pertinent data as might show a satisfactory degree of resistance to the disease. If there is no evidence of past or present resistance, the operation should be deferred.

2. *Physical Examination.* A clear contralateral lung as determined by the roentgen-ray is in itself not sufficient. Significance should be attached to

localized crepitant or subcrepitant râles elicited after cough in the hilus region or at the base of the better lung even when the roentgen film discloses no definite lesion. In one such case with basal râles a fatal termination from contralateral lower lobe involvement occurred two months after the completion of the third stage. The serial roentgen-ray films had given us a false sense of security, so that the auscultatory findings were too lightly regarded. The importance of careful and repeated chest examinations, preferably by more than one clinician, cannot, therefore, be over emphasized.

3. *Myocardial Integrity.* It is realized that even with all the instruments of precision now at our disposal it is exceedingly difficult to estimate a patient's cardiac reserve. Nevertheless, by means of a carefully taken history, and from the study of the pulse rate at rest, in the recumbent and upright positions, and following graded exercises, it is possible to form a reasonably accurate judgment as to the burden carried by the heart and as to the heart's ability to stand the immediate strain of a drastic operation and to later successfully accommodate itself to the intrathoracic changes occurring after a complete thoracoplasty. The blood pressure is an important guide. A pulse rate persistently above 100 with the patient at rest, and a systolic blood pressure below 100 are strongly suggestive of myocardial insufficiency.

4. *The Roentgenogram.* A study of serial films taken over a period of months or years is of the greatest help in determining accurately those mechanical factors interfering with healing which have recently been classically described by Pottenger.[20] An accurate knowledge of these mechanical factors enables the observer to decide upon the type and extent of the surgical operation. Not alone that—it visualizes the type of existing pathology, and shows whether the lesion is predominantly proliferative or exudative. The more it is proliferative, the greater the resistance. Finally, the film gives valuable information regarding the condition of the contralateral lung. The presence of a roentgen lesion without physical signs is a more frequent clinical experience than is the presence of physical signs without a demonstrable roentgen lesion.

From a study of these special features, the indications for thoracoplasty become clear-cut and logical. Briefly, they are:

1. Unilateral chronic fibro-ulcerative tuberculosis, in which conservative measures have failed and in which pneumothorax and phrenicectomy have proved ineffective.

2. The same type of lesion, with a limited contralateral involvement which has not been active for over a year.

3. Unilateral chronic cavitation when simpler measures have failed.

4. Recurring hemoptysis when the source of the bleeding is definitely ascertained and the contralateral lung is not under suspicion.

5. Tuberculous empyema when there is no tendency of the lung to re-expand following frequent aspirations. The presence of a bronchial fistula demands early intervention. A preliminary phrenicectomy is worth trying, as occasionally it alone closes the perforation and the lung thereafter slowly

reëxpands. If this does not occur within one or two months, there is very little to be gained from further waiting, especially if there is considerable toxic absorption. A moderate amount of chronic disease even with limited cavitation in the contralateral lung is not a contraindication to thoracoplasty for tuberculous empyema, for without operation the prognosis in this condition is invariably poor.

Limitations of Posterior Paravertebral Thoracoplasty

Since the major objective in the treatment of chronic pulmonary tuberculosis is the obliteration of pulmonary cavities, a thoracoplasty can be said to fail in its purpose if it does not effect this result. In 50 per cent of our thoracoplastic patients, although their general condition had greatly improved and many had attained normal working ability, there was a persistence of a small amount of bacillary sputum. No patient can be considered out of potential danger as long as the sputum remains positive for tubercle bacilli. Thick-walled apical cavities, and centrally located cavities with thick walls and a very thickened pleura are the principal causes for an imperfect collapse. Regeneration of the ribs, if the intervals between the stages of the operation have to be unduly prolonged on account of infection or the poor condition of the patient, frequently prevents a complete collapse. Anterolateral costectomy is advocated by Hedbloom [21] to meet such contingencies. It is applicable alike to incompletely collapsed pulmonary and to empyema cavities. This type of secondary operation will, in time, be more widely employed as the danger of imperfectly collapsed cavities comes to be more generally recognized. Our problem has been to convince the patient of the necessity of further surgery when he is enjoying good health and is free from symptoms except for the morning cough and slight expectoration. To obviate the possibility of a secondary operation, Bruns and Casper [22] have devised a new technic which is essentially a combination of an upper stage thoracoplasty and pneumolysis. It seems ideally indicated for an upper lobe lesion with a large thick-walled cavity. In our personal experience with two cases in which this operation was employed, the results have been very gratifying. For selected cases it will probably become the operation of choice.

Contraindications to Collapse Therapy

Although certain conditions interdicting the collapse of a lung by one of the three principal methods have already been touched upon, the general subject of contraindications is deserving of a separate discussion. The average patient between the ages of 15 and 50 with unilateral or nearly unilateral pulmonary disease rarely presents contraindications to pneumothorax. With the advent of insulin, diabetes no longer precludes pneumothorax. Our experience with pneumothorax in relatively young diabetics during the past five years has been gratifying. This does not hold true of

thoracoplasty. Dyspnea, if not toxic, cyanosis, emphysema and decompensated valvular heart disease contraindicate any form of collapse therapy. Well compensated mitral regurgitation is usually not a contraindication. In bronchial asthma, pneumothorax may be cautiously tried, possibly also phrenicectomy, but not thoracoplasty. In nephritis without evident impairment of the cardio-vascular system the two simpler measures are permissible. If renal function and blood chemical determination are within normal limits, thoracoplasty may be considered. Laryngeal tuberculosis, if not acute, and if not merely a local manifestation of miliary tuberculosis, does not contraindicate any form of collapse measure. In intestinal tuberculosis, if not too far advanced, pneumothorax or phrenicectomy may be employed but not thoracoplasty, unless the intestinal disease has been inactive for at least one year. Patients past the age of 40 do not tolerate collapse therapy well, especially thoracoplasty; yet, this is not an inflexible rule. A patient at the age of 45 or even 50 who has not been sick for more than five years and who, during that time, has had periods of remission enabling him to be up and about for several months at a time is often a better surgical risk than another patient 30 years old who has been sick 10 years and has been confined to bed the greater part of that time. As a matter of fact, it has been our practice, whenever we receive a patient who is suited for thoracoplasty and who has been confined to bed elsewhere for some time, to wean him gradually away from the bed and to assign him graded walking exercises for several weeks before proceeding with the operation; unless indeed the latter has to be done to meet an emergency, such as hemoptysis. Prolonged bed rest in patients of this type often causes a lowering of general muscular and myocardial tone. It is the flabby, irritable heart that constitutes one of the main dangers. The psychic state of the patient is also an important consideration. A fear-complex requires painstaking effort on the part of the clinician to overcome, not by coercion or persuasion, but by education. Close association between the successful postoperative case and the candidate for operation is often more helpful in overcoming the latter's apprehension than are the physician's efforts.

Results of Thoracoplasty

In only 2.4 per cent of all our patients, and 4.6 per cent of our unsuccessful pneumothorax cases, was thoracoplasty deemed a feasible procedure. In the desire to be of assistance to an otherwise doomed patient, certain relative contraindications were occasionally disregarded. That is probably why our results do not compare favorably with those of others. Our operative mortality, within one to four weeks, was 12 per cent. By a more rigid selection of cases, this figure has been reduced in the past year to a little over 7 per cent. Approximately 50 per cent have either experienced an apparent arrest of the disease, or have improved to such an extent as to enable them to do full time work. The observation period after the opera-

tion ranges from one to twelve years. In from 25 to 30 per cent of patients, in spite of improvement, varying degrees of invalidism persist. The cause of the invalidism in these cases is usually either the continuance of low grade tuberculous activity attributable as a rule to an incompletely collapsed cavity, or the presence of myocardial insufficiency or emphysema. The occurrence of new disease foci or the reactivation of old foci in the better lung has been very rare, especially in those whose sputum became free of tubercle bacilli. The results, therefore can be said to be excellent when one considers that these patients are at best sub-standard surgical risks. Considering the further fact that there is nothing else to offer them except several years of a hopeless sanatorium existence while they are waiting for the finale, thoracoplasty is a real boon to the far advanced case.

Summary

For over 13 years we have been employing collapse therapy in patients, the average duration of whose pulmonary disease has been five years, and of whom 70 per cent were far advanced cases with cavitation. In the past six years, the indications were extended and relative contraindications have been occasionally disregarded. Nevertheless, pneumothorax was applicable in only 15.67 per cent, phrenicectomy as an independent or supplementary procedure in 19 per cent and thoracoplasty in 2.4 per cent. Of 239 patients in whom pneumothorax was attempted, 63 or 26.3 per cent had complete pleural adhesions so that even a pocketed space could not be obtained. Since 75 per cent of all patients had had previous institutional or private treatment elsewhere, these figures would seem to indicate that either collapse therapy is not instituted early enough to make it of greater value or that many patients discharged as cured were actually only quiescent cases which later sustained relapses no longer amenable to rest treatment. Withal, our results have been essentially very satisfactory. Collapse therapy is justly considered the greatest achievement in the field of tuberculosis during the past two decades. It has made advanced pulmonary tuberculosis a treatable disease. To the properly selected patient, it offers a chance of recovery far greater than that which he can expect from any other form of treatment. It shortens the duration of the disease and makes recovery more certain. In the average patient, the choice of procedure should be first pneumothorax, second phrenicectomy, and third thoracoplasty. A patient under conservative treatment, even if he pursues a clinically favorable course, should have frequent roentgen-ray chest examinations and blood studies, especially erythrocyte sedimentation tests, to determine more accurately whether Nature's method is wholly adequate. If the indications for collapse therapy are favorable, it should be instituted without delay and before extension of the disease makes the patient unsuitable for such treatment.

The indications and contraindications have been emphasized, for they constitute the most important guides in the management of the advanced

case, though as yet no set rules are possible. The individualization of patients will always be essential to intelligent treatment, and above all clinical judgment is necessary. A knowledge of pneumodynamics is indispensable to both physician and surgeon, and both must render each other the closest coöperation in order to secure the best possible results for their patient. Finally, the psychological make-up of the patient must be carefully scrutinized and all hidden fears, doubts and prejudices unravelled and overcome. In no disease does the personal element, the tact, the kindliness of the physician, his willingness to give freely of his time to the patient count for as much as in tuberculosis. To be able to break unpleasant news in such a way as to make the patient see the more hopeful aspect of a perplexing situation is an art which can be acquired. It is the duty of the physician to inspire in his patient confidence in a proposed new form of treatment without necessarily concealing its hazards or actual dangers, and experience teaches how to do it. We confidently believe that by following closely such a program it is possible to obtain satisfactory results in even as unfavorable a disease as far advanced chronic pulmonary tuberculosis.

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CALCAREOUS AORTIC VALVULAR LESIONS*

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Stenosis of the aortic valve, with calcification, continues to attract the attention of clinicians and pathologists. The frequency with which this condition is found at autopsy, in contrast to the infrequency of its clinical diagnosis, and the unsettled state of opinion as to its etiology invite further study. To this end, 52 examples of aortic valvular disease have been selected from 4000 consecutive autopsies; these have been divided into significant groups, and subjected to clinico-pathological analysis. The results of this statistical study justify certain conclusions as to the etiology of this form of cardiac disease.

Survey of Literature

Aortic stenosis with calcification has been reported frequently and discussed from various points of view. Some of these case reports are presented without conclusions as to etiology.

Leclerc,[13] in 1905, reported two cases of aortic stenosis in which the maximum murmur was heard at the left of the sternum instead of in the usual aortic area. The other physical findings in both patients were typical of aortic stenosis and the diagnosis was verified by autopsy, both cases having a marked stenosis due to fusion and calcification of the cusps. The author accounted for the unusual location of the aortic murmur by leftward displacement of the heart.

Cabot,[4] in 1926, described a man of 47 years who had had a slowly progressing cardiac lesion since youth. At the time of admission he was *in extremis* and, with other murmurs, he had the typical murmur and thrill of aortic stenosis. Autopsy revealed aortic endocarditis with calcification, stenosis and insufficiency.

In 1931 Tuohy and Eckman[19] reported six cases of aortic stenosis, three of which had come to autopsy and these showed calcareous nodules in the cusps. These authors observed that there is associated with this type of aortic stenosis a demonstrable degree of insufficiency, that the valvular deformity is due to nodular calcium deposits in the media of the cusps, that this lesion may produce typical anginal attacks in the absence of any coronary lesions and that no other valvular lesion produces such marked left ventricular hypertrophy. They diagnosed the presence of the calcareous nodules during life.

Another group of writers have favored senile, or non-inflammatory, changes:

In 1904 Mönckeberg[15] discussed thoroughly the microscopic anatomy of the aortic valve in an attempt to explain the occurrence of sclerosis and calcification. He presented four groups of patients who did not die of cardiac disease but who showed at autopsy varying degrees of sclerosis of the aortic valve. He demonstrated, to his own satisfaction, that there is no direct association between atherosclerosis of the first

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part of the aorta and aortic endocardial sclerosis, but that the latter process, like the former, is a senile degenerative change.

In 1926 CLAWSON, BELL and HARTZELL [8] studied 15 hearts showing aortic stenosis due to calcareous nodules, with no satisfactory evidence of inflammatory origin. The position of these calcareous nodules did not correspond to that of the vegetations in active endocarditis and almost invariably the root of the aorta in these hearts was free from sclerotic lesions. Microscopically, the lesions consisted chiefly of masses of calcium salts, and decalcification left a homogeneous material. The surrounding connective tissue had the appearance of aortic atheroma with lipoid content. Frequently the surrounding tissue was vascular and showed mononuclear infiltrations. In one valve true cartilage and bone formation were noted. In other groups of hearts with known aortic endocarditis in various stages some were found in which calcareous nodules occurred which were identical with those in the above group and it could not be determined whether they had resulted from the inflammatory process or were merely coincidental.

In 1931 MARGOLIS, ZIELLESEN and BARNES [14] reported a series of 42 examples of calcareous aortic valvular disease, 34 of which were in males. These were selected because they showed this condition at autopsy, without significant degrees of involvement of other valves. The majority of the patients were over 50 years old. In only three was a typical murmur of aortic stenosis found clinically. At autopsy, the aortic valves were characterized by varying amounts of calcium deposition with stiffening or distortion of the cusps. Some showed stenosis or insufficiency or both. The characteristic feature was the involvement primarily of the aortic ring, or frequently only of the commissures, and in the more marked cases, extension onto the cusps. All but one case showed coronary sclerosis and 14 showed scattered myocardial fibrosis. There were no infarcts. Microscopical examination revealed myocardial hypertrophy and slight increase in interstitial tissue. Cellular infiltrations were lacking in all but one case. The calcium masses were surrounded by old, practically acellular, fibrous tissue except those which extended to the surface. There the exposed side was covered by fibrin. Most of the valves were free from cellular infiltrations, but in five instances there were small collections of lymphocytes and endothelial leukocytes in the cusps near the calcareous deposits. Some of the capillaries supplying the cusps showed medial proliferation with thickening of their walls. As to etiology, these authors suggested rheumatic fever, but added that the distribution and gross and microscopical appearances were atypical. They suggested also an inflammatory process in the arterioles of the valve ring leading to obliteration and subsequent ischemia, or a generalized or selective atherosclerosis involving these arterioles and producing the same result. They found no evidence that the explanation lay in a healed bacterial endocarditis and mentioned the fact that syphilis is not a likely cause since it is not particularly prone to lead to calcification.

Still another group have favored the common infectious diseases of childhood or tuberculosis as the etiological factor:

In 1909 GALLAVARDIN [10] wrote on a non-rheumatic aortic stenosis in young patients. He classified aortic stenosis as rheumatic, arterial (on a sclerotic basis), and congenital. To these three groups he added a fourth in which the etiology is obscure. This type is seen in young patients. There are indisputable physical signs and the lesion is purely, or at least predominantly, a stenosing one, due to fusion of the aortic cusps. It is perfectly tolerated for a long period of time. The author reported three cases of his own exemplifying this type of aortic lesion. Two of these were males; none had died when the paper was written. All had typical signs of aortic stenosis. He favored a slowly progressing chronic endocarditis during childhood and youth as the explanation and suggested tuberculosis or other infectious diseases of childhood as possible causes.

In 1921 GALLAVARDIN [11] wrote again on the same subject, presenting 10 additional cases. All of these were males (picked while examining young soldiers). All had typical physical signs of aortic stenosis except that in two the murmur was loudest at the left of the sternum. No autopsy reports were given.

In 1928 a case of non-rheumatic aortic stenosis in a young man of 24 was reported by ROUBIER and TOURNIAIRE.[18] There were definite clinical signs of aortic stenosis and no history of rheumatic fever or chorea. He had had cervical adenitis in childhood. Serological tests were negative for syphilis. Autopsy revealed a markedly enlarged heart (850 gm.), a recent adhesive pericarditis, and a hard stenotic and insufficient aortic valve. The under surfaces of the cusps were covered by cartilage-hard tissue containing nodules of calcium and the cusps were interadherent. These authors thought the lesion to be on an inflammatory basis and discussed as possibilities an old endocarditis of the ordinary type and tuberculosis. They mentioned also the possibility of syphilis.

A fourth group have favored syphilis as the cause of this disease:

In 1903 ARMAND-DELILLE and J. HEITZ [1] reported the case of a woman, aged 49 years, with a long history of gradually progressing symptoms of aortic stenosis. At autopsy a marked degree of calcification of the aortic valve with stenosis was found and, though they were unable to prove it, the authors thought syphilis was the cause.

In 1921 QUEYRAT and MOUQUIN [16] described a child slightly less than six years of age on whom they had made a diagnosis of congenital syphilis on physical stigmata in spite of negative serological tests. There was no history of rheumatic fever, chorea or scarlet fever. Physical examination revealed an undoubted aortic stenosis. These authors made a diagnosis of congenital aortic stenosis. No autopsy report was given.

The remaining authors have considered rheumatic fever a probable cause of calcification of the aortic valve:

In 1901 BARIÉ [2] wrote a paper on acquired aortic stenosis and chronic aortitis in children. In reviewing the literature he was struck by the frequency of this diagnosis. He found eight cases ranging in age from two to fourteen years. Five of these came to autopsy, and calcification of the aortic valve was described in two. Aortic stenosis was found in six cases and was accompanied by aortic insufficiency in five. One of these six was not proved by autopsy. In one case only was there mention of alteration of the other valves, and this was in a child who developed mitral and aortic murmurs during an attack of rheumatic fever. Barié reported his own observation of a boy, aged 15 years, who had had scarlet fever at eight. This patient had clinical evidence of aortic stenosis. In discussing the subject he distinguished two types of aortic stenosis in children: one coming on during the course of acute articular rheumatism with the lesions on the ventricular surfaces of the aortic cusps at their free margins, the aortic stenosis of endocardial origin; the other, associated with a chronic preëstablished aortitis. This, according to him, is the result of an arterial lesion which has extended to the valve cusps and is the more common. He concluded that in children it is more difficult to find the etiology than in adults in whom it can frequently be attributed to syphilis, typhoid fever, gout, lead poisoning, etc. In children, aortic stenosis is nearly always associated with other cardiopathy and is usually the sequel of chronic aortitis.

In 1930 DRAKE [9] summarized the clinical aspects of sclerotic changes in the aortic valve. In his discussion he suggested that rheumatic fever or atherosclerosis might be the etiology though senile changes fail to explain all cases. He found the lesion most often in elderly males and remarked that often there were no accompanying valvular lesions. He often observed the absence of a systolic thrill in these cases

and accounted for this on the basis of a weak myocardium. His cases had very little aortic insufficiency and consequently no abnormality in pulse pressure. They all showed a rather marked generalized atherosclerosis without marked involvement of the aorta.

In 1931 CHRISTIAN,[5, 6] in a paper entitled "Aortic Stenosis with Calcification of the Cusps," reported 21 cases ranging in age from 25 to over 60 years. Of these, 15 were males and all had no other valvular pathology. He found this lesion characterized clinically by its occurrence chiefly in males and relatively late in life; by its slow progression with cardiac decompensation appearing late; by the presence of a systolic thrill and harsh murmur over the aortic area, frequently accompanied by a softer blowing diastolic murmur; by considerable cardiac hypertrophy; by a decreased or normal pulse pressure, and by the absence of anything in the latter half of life to which the etiology might be attributed. At autopsy these hearts were characterized by increased weight, by marked narrowing of the aortic valve, and by thickened, often interadherent, cusps containing masses of calcium. In discussing etiology the author looked upon rheumatic fever as most likely since 11 of the 21 gave definite histories of this disease. Two others gave indefinite histories, and the remaining histories were probably unreliable because of the patients' condition or the lapse of time since the attack occurred. Against atherosclerosis with calcification as an explanation was the fact that most of the series showed little or no aortic atherosclerosis. He stated that the lesions in these cases bore no resemblance to syphilis of the aortic valve.

Also in 1931, CLAWSON [7] discussed an analysis of 161 cases with nonsyphilitic aortic valve deformity, either occurring alone or associated with deformities of other valves. From this analysis he concluded that severe aortic valve deformity is usually of the calcareous nodular variety, that a severe grade of aortic stenosis is common in this deformity and should frequently be diagnosed clinically, that compensation and tolerance of the lesion is a more important factor in explaining its frequent incidence in elderly people than is its being an old-age disease and that the frequency of a rheumatic history in these patients suggests an infectious etiology. The gross and microscopic findings also indicate an inflammatory origin. He found no support for the metabolic theory of origin and said the term "arteriosclerotic valve deformity" is a misnomer.

The foregoing summary reviews some of the more important writings in the literature on this subject. It might be well to mention also some of the work on the blood vessels of the heart valves, since this may be of importance in the etiology of aortic valvular lesions of the type under consideration.

In 1917 BAYNE-JONES [3] summarized the literature on this phase of cardiac anatomy and outlined a method of injection which he used to demonstrate blood vessels in the valves of human hearts. He found that in the semilunar valves the blood vessels arise from two sources: from the vasa vasorum of the aorta and pulmonary artery, and from the vessels of the auricular endocardium. From the former a few delicate vessels are given off at the line of attachment of the cusps to the wall of the artery and penetrate the valve for a short distance along its line of closure. Those from the latter source form a hedge-like plexus in the base of the cusp, and from this, delicate vessels pass upward for a distance of about one-half the width of the valve. He was unable to demonstrate vessels in the thin central portion of the valve cusps or in the noduli Arantii.

KUGEL,[12] in 1928, in an article entitled "Anatomical Studies on the Coronary Arteries and Their Branches," discussed the *arteria anastomotica auricularis magna*. He demonstrated this vessel by injection methods and described it as a large anasto-

motic artery linking the left and the right coronaries. It is constant in its occurrence, though subject to slight variations in its course. It supplies branches to the aortic cusp of the mitral valve and to the aortic valve cusps (when vessels are found in these sites), as well as to the commissures of the aortic valve and to the base of the aorta.

Later in 1928 RITTER, GROSS, and KUGEL [17] presented a study of 14 cases out of 700 examined having *arteriae valvulares*, these 14 showing no evidence of any previous inflammatory process.

MATERIAL

For this study I have selected 52 cases showing aortic valve lesions. These have been divided into four groups, the first of which includes those showing sclerosis and calcification of the aortic valve with no obvious etiology. This group is further divided into two subgroups, one of which includes the cases showing no other essential valvular lesions and the other, those showing also other valvular changes. In group II are those cases in which there is definite pathological evidence of syphilis as an etiologic factor. Group III contains those cases with clinical or pathological evidence of rheumatic fever as the causative factor. In group IV there are a few cases showing active subacute bacterial or ulcerative aortic endocarditis without involvement of the other valves. Groups II, III, and IV have been selected for comparison with group I. Group I contains 29 cases, 10 of which show involvement of the aortic valve alone. In group II there are nine cases. Group III contains 11 while there are but three in group IV. The aortic valves in group IV show no calcification, these cases being included in order to obtain a comparison with active inflammatory aortic lesions.

In order to save space these various groups will be presented collectively with the incidence of various features given by number of cases. In the tables the same information is presented as percentages of the total number in the group to facilitate comparison.

GROUP I A. UNDETERMINED ETIOLOGY, AORTIC VALVE ALONE AFFECTED

Of the 10 cases in group I showing no involvement of the other valves, seven were males. The average age was 52 years, the youngest patient being 30 and the oldest 84. Clinical records were available on only eight of the 10 and of these, six complained of undoubted cardiac symptoms. One had symptoms which might have been cardiac, but could be explained on the basis of the severe anemia which was also present. In one case the complaint was definitely non-cardiac. In the histories of this group of eight patients the following infections were recorded:

Infection	Number of Cases	Percentage of Group (8 cases)
Measles	4	50
Pneumonia	3	37½
Rheumatic fever	2 (1 questionable)	25
Scarlet fever	2	25
Diphtheria	1	12½
Typhoid fever	1	12½
Gonorrhea	1	12½
Influenza	1	12½
No infections	1	12½

In these eight records the physical examination showed cardiac enlargement in six. Seven had a systolic cardiac murmur and in four of these the murmur was best heard at the base. In one case there was an accompanying systolic thrill. One patient had a diastolic mitral murmur and one had no cardiac murmur. The average blood pressure of the six cases in which it was recorded was approximately 120 mm. Hg systolic and 82 diastolic, the highest systolic pressure being 138. The lowest diastolic pressure was 10, in a patient *in extremis*. The three cases in which the result of the Kahn test was reported showed negative results. The cause of death as determined at autopsy was cardiac disease in four instances; in two, pernicious anemia; in three, carcinoma, and in one, pneumonia. Thus in six cases the cause of death can be considered non-cardiac.

At autopsy all of these hearts showed calcification of the aortic valve similar to that seen in figure 1. Nine showed cardiac enlargement. Seven had aortic stenosis of varying severity, and four of the group had an associated aortic insufficiency. Three showed no aortic stenosis or insufficiency. One heart showed adhesive pericarditis, while the others showed no pericardial abnormality save a soldier's spot in one and an increase in fluid in another.

Analysis of the microscopic studies of these ten hearts reveals no hypertrophy of the muscle fibers in four, slight in four, moderate in one and marked in one. In one case there was no atrophy of the muscle fibers, in eight atrophy was slight, and in one it was moderate in degree. None of the 10 showed hypoplastic fibers. Seven showed a slight degree of myocardial fibrosis, two showed a moderate degree and one a marked fibrosis. The distribution of this fibrosis was patchy in eight and diffuse in two. In no case was it perivascular. In four cases its character was fibroblastic, in five it was hyaline, one of these showing small fibroblastic areas. In one it was myxomatous with hyaline change in some areas.

Active cellular infiltrations were present in the myocardium to a slight degree in five of the cases. In two of these the infiltrations were perivascular. The remaining five hearts showed no infiltrations. In two, sections showed no interstitial tissue increase; six showed slight increase; one, a moderate, and one a marked increase. No Aschoff nodules were found in any of the group. Endocardial sclerosis, aside from that in the aortic area, was not present in two cases, only slight in three, moderate in three, and marked in two. Extension of the endocardial sclerosis into the myocardium was observed in varying degrees in six hearts. Five hearts revealed no fatty infiltration of the myocardium, two revealed a slight degree and three a moderate degree. Degenerative fatty infiltration was absent in one, slight in three and moderate in six. The small coronary vessels showed no sclerosis in seven cases, a slight degree in two and a moderate degree in one. The medium-sized coronary branches were negative in three, slightly sclerotic in five and moderately sclerotic in two. The large coronaries showed a slight degree of sclerosis in six; a moderate degree in three, one of which showed partial occlusion, and a marked degree in one.

FIG. 1. Group I A. Male, aged 30. Severe aortic stenosis with marked calcification of cusps and left ventricular hypertrophy.

GROUP I B. UNDETERMINED ETIOLOGY, OTHER VALVES ALSO ALTERED

The remaining 19 cases in group I are those which, in addition to aortic valve sclerosis, showed other valvular lesions. Of these, 12 were males. The average age for the group was 60 years; the youngest patient was 40 and the oldest was 98. The record on one of these patients was not available, so the percentages on the clinical findings are computed on a total of 18. Ten gave complaints which were definitely cardiac. The remainder gave

non-cardiac complaints. The histories revealed the following infections in these patients:

Infection	Number of Cases	Percentage of Group (18 cases)
Measles	8	44
Scarlet fever	6	34
Mumps	5	28
Whooping cough	4	22
Chicken pox	4	22
Rheumatic fever	3	17
Diphtheria	3	17
Smallpox	3	17
Quinsy	2	11
Tonsillitis or sore throat	2	11
Influenza	2	11
Typhoid fever	2	11
Malaria	1	6
Pneumonia	1	6
Hard chancre	1	6
"Usual childhood diseases"	2	11
No infections	5	28

Physical examination revealed cardiac enlargement in 10 of the 18. A systolic murmur was heard in 14; in seven of these it was loudest at the base and in the other seven it was best heard at the apex. Five had a diastolic murmur. Seven had a greater or lesser degree of sclerosis of the peripheral vessels. The average blood pressure of the group was 153 mm. Hg systolic and 94 diastolic, the highest systolic being 224, and the highest pulse pressure 104. In the 12 cases on which the Wassermann or Kahn test was done there were negative reports.

The causes of death in these 19 cases, based on the autopsy findings, were as follows: six, malignancy (five carcinomas, one hypernephroma); five, arteriosclerosis (including cardiopathia arteriosclerotica); four, mitral or aortic valvular disease, or both; one, hemiplegia; one, pneumonia; one, pulmonary tuberculosis; and one, pansinusitis.

Examination of the hearts at autopsy revealed definite cardiac enlargement in 12, the heaviest heart weighing 770 gm.; five showed an old patchy epicarditis. Twelve showed no stenosis of either the mitral or aortic valve. Seven showed valvular stenosis as follows: mitral valve alone, four (one with insufficiency also); aortic valve alone, one; and both valves, two.

The microscopic findings are summed up as follows: hypertrophy of muscle fibers was absent in six, slight in 10, and moderate in three. Atrophy was absent in four, slight in six, and moderate in nine. Hypoplasia of the muscle fibers was absent in 18 and present to a moderate degree in one. The amount of fibrosis of the heart wall was considered slight in nine cases and moderate in 10. This connective tissue had a patchy distribution in 12 cases, in one of which it was perivascular in some areas. It was diffuse in two cases and especially perivascular in five. Its character was predominantly fibroblastic in seven cases in one of which it was hyaline in areas. It was predominantly hyaline in 12 cases, in three of which there were fibroblastic areas, one with myxomatous regions.

Active cellular infiltrations were not found in 11 of these cases; they were considered slight in seven and moderate in one. In four of these they were perivascular in distribution. Increased stroma was absent in one case, slight in eight and moderate in 10. No Aschoff nodules were found in these 19 cases. Endocardial sclerosis other than valvular was not found in five cases, was only slight in six, moderate in seven and marked in one. In 16 it extended into the myocardium in varying degrees.

Fatty infiltration was absent in 12 cases, slight in four and moderate in three. Degenerative fatty infiltration was absent in two cases, slight in nine, moderate in five and marked in three. The small coronary vessels showed no sclerosis in 14 cases; the medium-sized ones, none in nine cases, and the large ones, none in two cases. A slight degree of sclerosis was observed in the small ones in five cases, in the medium-sized ones in five cases, and in the large ones in 10 cases. A moderate degree was found in the medium-sized vessels in five cases and in the large ones in one case. Marked coronary sclerosis was observed in six cases, in all of which it was present only in the larger branches.

Group II. Etiology Determined to Be Syphilis

In group II there are six males and three females. The average age of the group was approximately 49 years, the oldest individual being 68 and the youngest, 18. In one patient the clinical record was not available and in another the complaint was not obtained because the patient was in a stuporous condition on admission. Of the seven on whom complaints were recorded three were non-cardiac and four, cardiac. The eight histories reviewed revealed the following infections:

Infection	Number of Cases	Percentage of Group (8 cases)
Influenza	2	25
Hard chancre	2	25
Gonorrhea	2	25
Measles	1	12½
Scarlet fever	1	12½
Whooping cough	1	12½
Quinsy	1	12½
Tonsillitis or sore throat	1	12½
Typhoid fever	1	12½
Malaria	1	12½
Pneumonia	1	12½
Rheumatic fever	1	12½
Running ear	1	12½
"Usual childhood diseases"	2	25
No infections	2	25

Physical examination revealed cardiac enlargement in seven of the eight whose records were available. In one of these it was recorded as slight; in the other case there was no enlargement. Systolic murmurs were heard in six cases, in two of which the maximum intensity was at the base. In two cases a diastolic murmur was heard at the apex and in one of these there was an accompanying thrill. A presystolic murmur at the apex was noted

in one case. In three cases diastolic murmurs were heard at the base. Results of the Kahn test were reported on two; one, negative, and the other, two plus. The average blood pressure in the five cases of the group in which it was recorded was 133 mm. Hg systolic and 85 diastolic, the highest systolic pressure being 160 and the highest pulse pressure being 68.

The causes of death as determined at autopsy were as follows: carcinoma of prostate in one instance; syphilitic heart disease in two; syphilis of the aorta in three, in one of which there was aortic valvular insufficiency, in another an accompanying syphilitic involvement of the myocardium and aortic valve, and in the third an aortic aneurysm. One death was due to aortic stenosis and insufficiency with a generalized atherosclerosis; another was a thymico-lymphatic death; and another was due to rheumatic heart disease. In this last case it was determined microscopically that syphilis also was a factor.

The hearts in these cases were found enlarged at autopsy in eight instances, the largest one weighing 1350 gm. There was an area of adhesive pericarditis in one case, soldier's spots in three and hydropericardium in one. Bilateral ventricular mural thrombi were found in one. Both the aortic and mitral valves showed sclerosis and calcification in three cases and in one of these there was thickening of the tricuspid flaps also. In six cases the valvular involvement, except for relative insufficiency, was limited to the aortic valve. There was aortic stenosis in three and in two of these there was an associated insufficiency. Aortic insufficiency without stenosis occurred once and one case showed mitral stenosis and insufficiency. Four hearts showed no valvular stenosis or insufficiency.

Analysis of the microscopic studies on this group reveals no hypertrophy of the muscle fibers in four cases, slight hypertrophy in three, and moderate in two. Atrophy of the muscle fibers was absent in two, slight in four, and moderate in three. Hypoplasia was absent in all nine cases. The degree of fibrosis of the myocardium was slight in two cases, moderate in six, and marked in one. This connective tissue was distributed diffusely in eight cases (two showing a patchy distribution in areas), and had a patchy distribution in one case. It was hyaline in five cases (two showing fibroblastic areas), myxomatous with fibroblastic areas in one, and fibroblastic in three (one showing hyaline areas). Active cellular infiltrations were found to a slight degree in three cases, to a moderate degree in five and to a marked degree in one. These were perivascular in distribution in five cases. A slight degree of increase of stroma was observed in two cases and a moderate degree in seven. No Aschoff nodules were found in any of this group.

All nine cases showed endocardial sclerosis in addition to that on the valves. In three it was slight in amount; in five it was moderate, and in one, marked. In two cases there was no extension into the myocardium. The others showed varying degrees of extension. Fatty infiltration of the myocardium was absent in five cases, slight in three and marked in one. Degenerative fatty infiltration was slight in two cases, moderate in four and

marked in three. The small coronary vessels showed no sclerosis in five cases, a slight degree in two and a marked degree in two. The medium-sized ones showed no sclerosis in six, a slight degree in two and a moderate degree in one. The larger vessels showed no sclerosis in three, slight sclerosis in four and marked in two.

Group III. Etiology Determined to Be Rheumatic Fever

Of the 11 cases in group III, six were males. The average age in this group was 26 years, the youngest patient being 13 and the oldest 52 years old. All of these patients gave complaints referable to cardiac disease. The following table gives a summary of the infections found in their past histories:

Infections	Number of Cases	Percentage of Group (11 cases)
Rheumatic fever, Chorea, Joint and cardiac symptoms	5, 1	55
Measles	6	55
Influenza	6	55
Tonsillitis or sore throat	4	36
Pneumonia	3	27
Chicken pox	3	27
Whooping cough	2	18
Mumps	2	18
Diphtheria	2	18
Gonorrhea	1	9
Scarlet fever	1	9
Typhoid fever	1	9
Malaria	1	9
Catarrhal jaundice	1	9

Cardiac enlargement was found clinically in all of the group. Cardiac murmurs were heard in every case. Systolic murmurs were heard in nine cases, usually over the entire precordium, but confined to the base in three cases. In one case there was an associated systolic thrill. Diastolic murmurs were heard in ten cases. These were most frequently associated with systolic murmurs, but in a few instances occurred alone at the base or apex. In three cases diastolic thrills were noted. The average blood pressure of the four cases in which it was recorded was 141 mm. Hg systolic and 38 diastolic (in one of these the diastolic pressure was 0). A negative Kahn test was recorded in six cases, no record being found in the other five.

The causes of death as determined at autopsy were rheumatic heart disease in nine, in one of which there was also the possibility of gonorrheal endocarditis; vegetative endocarditis in one, and chronic mitral and aortic thromboendocarditis in the other one. Autopsy revealed cardiac enlargement in all of the group, synechia cordis in three, partial adhesive pericarditis in one, patches of epicardial sclerosis in one, and hydropericardium in one. Vegetations were found on both the aortic and mitral valves in three cases, on the aortic valve alone in two cases, and on the mitral alone in one case. In five there were no vegetations. In no case was there aortic valve involve-

ment without involvement also of some of the other valves. The aortic valve lesions varied from slight sclerosis to marked calcification with interadherent cusps. There was no aortic stenosis in the group.

Summary of the microscopic findings in this group shows absence of muscle hypertrophy in three hearts, slight hypertrophy in five and moderate hypertrophy in three. Atrophy of the muscle fibers was absent in two, slight in four and moderate in five. Hypoplasia was not observed in any. Fibrosis of the myocardium was slight in three cases, moderate in six and marked in two. The distribution of the fibrosis was predominantly perivascular in seven, four of these showing diffuse areas and two showing areas in which the distribution was patchy. Four showed a predominantly diffuse distribution, two having areas with a perivascular and three, a patchy distribution. The connective tissue was hyaline in six hearts, three of these showing fibroblastic areas; fibroblastic in four, two of these showing hyaline areas; and myxomatous in one, this one showing also some fibroblastic areas. Active inflammatory infiltrations were not found in three cases. They were slight in five, moderate in two and marked in one. In seven the infiltrations had a perivascular distribution. An increase of stroma was observed in all 11 cases; in three it was slight in amount, in six it was moderate and in two it was marked. Aschoff nodules were not found in seven cases; in one case only a few were found, and in three they were moderate in number. Endocardial sclerosis, other than valvular, was slight in amount in three cases, moderate in seven and marked in one. It extended into the myocardium slightly in five and moderately in six.

Fatty infiltration of the myocardium was absent in two cases, slight in six, moderate in two and marked in one. Degenerative fatty infiltration was slight in three cases, moderate in seven and marked in one. The coronary vessels were relatively free from sclerosis. The small and medium-sized branches showed none in nine cases and the large ones, none in four cases. The small branches showed a slight degree of sclerosis in one and a moderate degree in one, while the medium-sized branches showed only a slight degree in two cases. The large vessels showed a slight degree in five and a moderate degree in two. In one case one of the large vessels was partially occluded by a sclerotic plaque.

Group IV. Active Vegetative and Ulcerative Aortic Valvulitis

The three cases in group IV are studied merely for comparison in the hope of discovering the etiology of calcification of the aortic valve. Two were males and the average age was 34 years, the youngest being 26 and the oldest, 47. One of these patients entered the hospital complaining of chills and fever and swelling of the feet and ankles. The other two had definite cardiac complaints, one being *in extremis*. The infections that these patients remembered having had are given in the following table:

Infections	Number of Cases	Percentage of Group (3 cases)
Measles	2	66⅔
Whooping cough	2	66⅔
Chicken pox	1	33⅓
Mumps	1	33⅓
Sore throat	1	33⅓
Quinsy	1	33⅓
Scarlet fever	1	33⅓
Diphtheria	1	33⅓

Physical examination revealed cardiac enlargement in two, and systolic and diastolic murmurs at both the apex and base in all three cases. The result of the Wassermann test, reported on one record, was negative. Blood culture was positive for *Streptococcus viridans* in one case and not reported on the others. The average blood pressure was 116 mm. Hg systolic and 51 diastolic in the two patients for whom it was recorded. One of these had a pulse pressure of 80.

The causes of death as determined at autopsy were subacute ulcerative aortic endocarditis, vegetative aortic endocarditis, and subacute vegetative and ulcerative aortic endocarditis with mycotic aneurysm. Cardiac enlargement was found in two of the three at autopsy. Two had a patchy adhesive pericarditis and one an hydropericardium. The aortic and mitral valve lesions varied from vegetative to ulcerative in type, the aortic valve in one showing a mycotic aneurysm. One aortic valve was bicuspid. Postmortem blood culture was positive for *Streptococcus viridans* in one instance (not the case with the positive antemortem culture).

Summary of the microscopic findings in group IV reveals no hypertrophy of the muscle fibers in one case and moderate hypertrophy in two. Atrophy was absent in one, slight in one and moderate in one, while hypoplasia was absent in all three. Myocardial fibrosis was slight in amount in two cases and moderate in amount in one. Its distribution was diffuse in one, patchy in one and perivascular in one. It was fibroblastic in all three. Active inflammatory infiltrations of the myocardium were found in one of the three cases where they were moderate in extent. In this case they were not perivascular in distribution. Increased stroma was considered slight in two cases and moderate in one. Aschoff nodules were found in none of these cases.

Endocardial sclerosis was absent in one case, slight in amount in one and moderate in one. In two it did not extend into the myocardium and in one showed only slight extension. Fatty infiltration of the myocardium was slight in all three cases. Degenerative fatty infiltration was moderate in all. Sclerosis of the small, medium-sized, and large coronary vessels was absent in all three cases.

Comparative Summary

To facilitate the comparison of the foregoing groups of cases tables are given. (See tables 1, 2 and 3.) In addition a brief comparative summary seems necessary. Sclerosis and calcification of the aortic valve seem to

TABLE I

Percentage Distribution of Clinical Findings in Four Groups of Aortic Valvular Lesions

Group	Sex		Average Age	Complaints		History of Infections						
	Male	Female		Cardiac	Non-Cardiac	Measles	Scarlet Fever	Rheumatic Fever	Diphtheria	Tonsillitis	Gonorrhea	Syphilis
I A	70	30	55	75	25	50	25	12½	12½	0	12½	0
I B	63	37	60	55	45	44	34	17	17	11	0	6
II	66⅔	33⅓	49	57	43	12½	12½	12½	0	12½	25	25
III	55	45	26	100	0	55	9	55	18	36	9	9
IV	66⅔	33⅓	34	66⅔	33⅓	66⅔	33⅓	0	33⅓	33⅓	0	0

TABLE I (*Continued*)

Group	Physical Examination						Cause of Death		
	Cardiac Enlargement	Systolic Murmur	Diastolic Murmur	Systolic Thrill	Diastolic Thrill	Average Blood Pressure	Pneumonia	Malignancy	Cardiac Disease
I A	75	87½	12½	12½	0	120/82	10	30	40 *
I B	55	78	28	0	0	153/94	5	30	47 †
II	87½	75	75	0	12½	133/85	0	11	78 ‡
III	100	82	91	9	27	141/38	0	0	100
IV	66⅔	100	100	0	0	116/51	0	0	100

* The other two died from pernicious anemia.

† The remaining 18 per cent died from hemiplegia, pulmonary tuberculosis and pansinusitis.

‡ The other was considered a thymicolymphatic death.

occur slightly more frequently in the male than in the female. The average age of these groups varies somewhat, that of the group of rheumatic fever cases being the lowest, the active endocarditis group next in the age scale, the syphilitic group next and the group of unknown etiology highest. In a rough way then, these four groups can be separated according to the average age at which death occurred.

The complaints of the patients upon entering the hospital indicate that they sought medical attention primarily for heart disease, more often than for remote diseases. Study of the incidence of the various infections in

these groups reveals nothing by which any one of them can be characterized. Measles occurred in about one-half of each group except group II, in which there was an incidence of but 12.5 per cent. The incidence of scarlet fever varied from about one-eighth to one-third, the lowest being in group III, the rheumatic fever group, and the highest being in the second division of group I. This disease has been blamed for the occurrence of aortic endocardial sclerosis, but its incidence in our series is not sufficiently high to lend much weight to this opinion. The incidence of a history of rheumatic fever varied from about one-eighth to one-fourth except in the rheumatic fever group where it was slightly over one-half. It was approximately the same in the syphilitic group as in the unknown group, so these figures do not point conclusively to rheumatic fever as the etiology in group I. The incidence of

TABLE II

Percentage Distribution of Gross Pathological Cardiac Findings in Four Groups of Aortic Valvular Lesions

Group	Cardiac Enlargement	Aortic Valve Calcification	Aortic Stenosis	Aortic Insufficiency	Mitral Valve Calcification	Mitral Stenosis	Mitral Insufficiency	Pericarditis
I A	90	100	70	40	0	0	0	10
I B	63	100	16	0	47	32	5	26
II	89	100	33	33	33	11	11	44
III	100	9	0	0	45	45	27	45
IV	$66\frac{2}{3}$	$66\frac{2}{3}$	$66\frac{2}{3}$	$33\frac{1}{3}$	0	0	0	$66\frac{2}{3}$

diphtheria is likewise as high outside of group I as within it except for group II in which no history of diphtheria was obtained. Tonsillitis, or sore throat of frequent occurrence, was higher in its incidence outside of than inside of group I. History of gonorrhea and syphilis did not occur more frequently among the cases in group I than in the other groups in spite of the known fact that gonorrheal endocarditis frequently involves the aortic valve alone. Typhoid fever, which has also been cited as a possible etiologic factor, occurred in about one-eighth of each of the groups except in group IV where it did not occur at all. It should be remembered, also, that the members of our group I, having the highest average age, have a better chance to have had these infections, and should, therefore, have a higher incidence of them. Another point to be considered is that the older patients may have forgotten the infections of earlier life.

On physical examination a majority of all the groups showed cardiac enlargement, and a systolic murmur was heard in over three-fourths of every group. It is surprising that such a high proportion showed clinical signs of

valvular lesions when we consider that a much lower percentage actually showed valvular stenosis or insufficiency at autopsy. The importance of the systolic thrill in making a clinical diagnosis of calcareous aortic valvular disease with stenosis has been emphasized in the literature. In this series of patients including all four groups, it was recorded only twice, aortic stenosis being found at autopsy 16 times. In groups II, III and IV a diastolic thrill was observed five times, mitral stenosis being found at autopsy six times in these groups. The average blood pressures of the several groups were not

TABLE III

Percentage Distribution of Microscopic Findings in Four Groups of Aortic Valvular Lesions

Group	Hypertrophy				Atrophy				Fibrosis				Distribution of Fibrosis			Character of Fibrosis		
	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Patchy	Diffuse	Perivascular	Fibroblastic	Hyaline	Myxomatous
I A...	40	40	10	10	10	80	10	0	0	70	20	10	80	20	0	40	50	10
I B...	32	53	15	0	21	32	47	0	0	47	53	0	64	10	26	37	63	0
II.....	45	33	22	0	22	45	33	0	0	22	67	11	11	89	0	33	56	11
III....	27	46	27	0	18	36	46	0	0	27	55	18	0	36	64	36	55	9
IV.....	33⅓	0	66⅔	0	33⅓	33⅓	33⅓	0	0	66⅔	33⅓	0	33⅓	33⅓	33⅓	100	0	0

TABLE III (*Continued*)

Group	Active Infiltrations				Distribution of Infiltrations		Increased Stroma				Aschoff Nodules		Endocardial Sclerosis				Extension into Myocardium of Endocardial Sclerosis	
	Absent	Slight	Moderate	Marked	Diffuse	Perivascular	Absent	Slight	Moderate	Marked	Absent	Present	Absent	Slight	Moderate	Marked	Absent	Present
I A...	50	50	0	0	80	20	20	60	10	10	100	0	20	30	30	20	40	60
I B...	58	37	5	0	79	21	5	42	53	0	100	0	26	32	37	5	16	84
II.....	0	33	56	11	44	56	0	22	78	0	100	0	0	33	56	11	22	78
III....	27	46	18	9	33	67	0	27	55	18	64	36	0	27	64	9	0	100
IV.....	66⅔	0	33⅓	0	100	0	0	66⅔	33⅓	0	100	0	33⅓	33⅓	33⅓	0	66⅔	33⅓

TABLE III (*Continued*)

Group	Fatty Infiltration				Degenerative Fatty Infiltration				Coronary Atherosclerosis											
									Small Branches				Medium-sized Branches				Large Branches			
	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked
I A...	50	20	30	0	10	30	60	0	70	20	10	0	30	50	20	0	0	60	30	10
I B...	63	21	16	0	10	48	26	16	74	26	0	0	48	26	26	0	10	53	5	32
II.....	56	33	0	11	0	22	45	33	56	22	0	22	67	22	11	0	33	45	0	22
III....	18	55	18	9	0	27	64	9	82	9	9	0	82	18	0	0	36	46	18	0
IV.....	0	100	0	0	0	0	100	0	100	0	0	0	100	0	0	0	100	0	0	0

at wide variance when the average ages of the groups are considered. The highest systolic pressure in the entire series was 224 in a woman of 63 with a marked generalized atherosclerosis.

The causes of death were predominantly cardiac in all except group I where more frequently the cause was remote. Autopsy revealed a slightly higher percentage of cardiac enlargement in group I than was determined clinically but in the other groups the agreement was very close. The high proportion of these cases having cardiac enlargement is in accordance with the findings of other investigators on this subject. The fact that calcification of the aortic valve was not found in 100 per cent of groups III and IV has been explained before. The occurrence of aortic stenosis was considerably more frequent in group I, especially in subdivision A. This may be accounted for partly on the basis of age, the sclerosing process having had more time to produce stenosis in the older patients. Aortic insufficiency as found at autopsy was relatively infrequent except in the syphilitic group where it occurred as frequently as did stenosis. Calcification of the mitral valve, absent from group I A by selection, is much less common than calcification of the aortic valve in the remainder of the series except in the rheumatic fever group where it is five times more common. Naturally the occurrence of mitral stenosis and insufficiency bears a similar relation to aortic stenosis and insufficiency. The occurrence of pericarditis in any form was much less common in group I A, being more prevalent in those groups in which there were more active lesions of an inflammatory nature and especially in the rheumatic fever group.

Comparison of the microscopic findings in the various groups reveals strikingly little variation in the amount of hypertrophy of the myocardium observed. There is a rough proportion between this and the degree of aortic

stenosis or the severity and chronicity of the cardiac disease. Likewise atrophy of the myocardium is not distinctive in any particular group but seems to be proportionate to the average age of the group. Myocardial fibrosis showed the highest incidence in the syphilitic group and next highest in the rheumatic fever group. It was present to a marked degree in only one case of group I and this was a patient with arteriosclerotic heart disease. The fibrosis had a patchy distribution in the majority of the cases in both divisions of group I. In the syphilitic group its distribution was predominantly diffuse, while in the rheumatic and ulcerative groups the majority showed perivascular distribution. The character of the fibrosis was predominantly hyaline in every group except number IV, where it was fibroblastic.

Active infiltrations in the myocardium were not outstanding in group I, though they were considered a little more prominent in that part of the group showing involvement of other than the aortic valve. In the other groups active infiltrations were present in the majority of the cases except in group IV. These infiltrations showed a predominantly diffuse distribution in group I, a slight tendency to perivascular distribution in the syphilitic group and a fairly marked tendency in this direction in the rheumatic group. Increased stroma was found to a considerable extent in every group but was most marked in the rheumatic group. The syphilitic group was next in order. Aschoff nodules were found only in group III, and even here in a relatively low percentage of the cases.

Sclerosis of the endocardium was found to be fairly constant all through the series, being most marked in group I A; and in the great majority of cases in which it occurred there was extension into the myocardium. Fatty infiltration of the myocardium was absent in half or more of the cases in groups I and II, being a more prominent feature of the rheumatic and ulcerative groups in spite of the lower age figures in these groups. Degenerative fatty infiltration, on the other hand, was present in nearly every case of the entire series. It was most marked in groups II, III, and IV.

Atherosclerosis of the small coronary arterial branches was absent in nearly three-fourths of the cases in group I. A smaller number of the medium-sized branches, however, showed negative findings, over half of the group presenting atherosclerosis either to a slight or a moderate degree, but none to a marked degree. The larger branches in group I showed a fairly marked sclerosis, more than did any other group. In group II the small branches were free from sclerosis in slightly over half of the cases, but half of those showing sclerosis showed it to a marked degree. In this group, also, the medium-sized branches were relatively free from sclerosis and the large branches showed a much less degree than did those of group I. In groups III and IV sclerosis of the small and medium-sized branches was rare indeed. The large branches in group III showed a slight degree of sclerosis while those of group IV showed none.

Discussion and Conclusions

Consideration of the ages of the groups of cases studied indicates that those with sclerosis of the aortic valve of the type whose etiology is not clear live longer than those of known syphilitic or rheumatic origin. This finding cannot be used to rule out rheumatic fever or syphilis in the older group, however, since this group may have had stronger constitutions, or have been less severely attacked by the causative disease, or attacked later in life.

The possibility that some of the frequent infections found in the past

Fig. 2. Group I A. Female, aged 52. Aortic valve cusp showing calcareous nodules. Patient had a severe aortic stenosis. (×7.)

histories could be etiologic factors in this type of stenosis of the aortic valve seems unlikely since there are none which specifically characterize our unknown group. While too much stress should not be placed on histories, it is significant that rheumatic fever was mentioned by but 12.5 per cent of the members of this group.

The clinical findings in these groups of patients need not be discussed further except to say that, unless there is a fairly marked aortic stenosis present, sclerosis of the aortic valve with calcification may not be recognized by the clinician, unless perchance it be detected by the roentgenologist. The blood pressures in this series of patients were not distinctive in any one group.

FIG. 3. Greater magnification of calcareous nodule seen in figure 2 at base of cusp. Note absence of evidence of inflammatory reaction. (× 45.)

When the microscopical studies are considered and group I A compared with the other groups, there is noted strikingly little evidence of inflammatory processes in group I A (figures 2, 3 and 4). Pericarditis was less common in this group, myocardial fibrosis was less prevalent and in the case where it did occur to a marked degree could be accounted for on the basis of arteriosclerosis. The distribution of the fibrosis found in group I A was more that of arteriosclerotic cardiopathy than of any form of infectious

myocarditis of which we have knowledge. Active infiltrations of the myocardium were not a characteristic feature of group I. They were slightly more noticeable in I B than in I A, however, and this fact, together with the slightly greater incidence of fibrosis in I B, is the only point of difference observed to indicate that such a separation is justified. Where active infiltrations occurred in group I they were usually diffuse in distribution which is against rheumatic myocarditis in its active stage. The cellular infiltra-

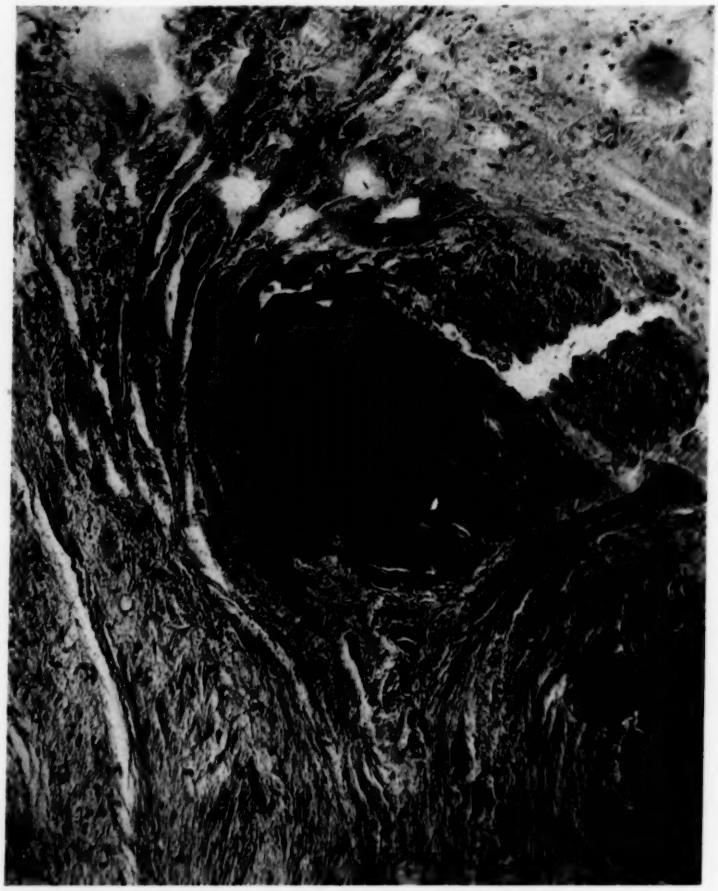

FIG. 4. Greater magnification of one of the calcareous nodules seen in figure 2. Note absence of evidence of inflammatory reaction. (×60.)

tions about the calcium deposits in the aortic valve were similar to those seen in the aorta about calcareous deposits (figure 5). Even though increased stroma was fairly prevalent in group I it was less so than in the other groups. The absence of Aschoff nodules from group I is excellent evidence against rheumatic fever as the etiology. To be sure, they were not found in all of the cases in the rheumatic group, but examination of many more sections

from the cases where they were not demonstrated would very likely have raised the percentage considerably. On the other hand, group I contains many more cases, and if the etiology were rheumatic fever in this group some of these hearts must surely have contained these pathognomonic nodules.

Endocardial sclerosis, aside from that in the aortic area of these hearts, was considered. It was found most marked in group I where there was

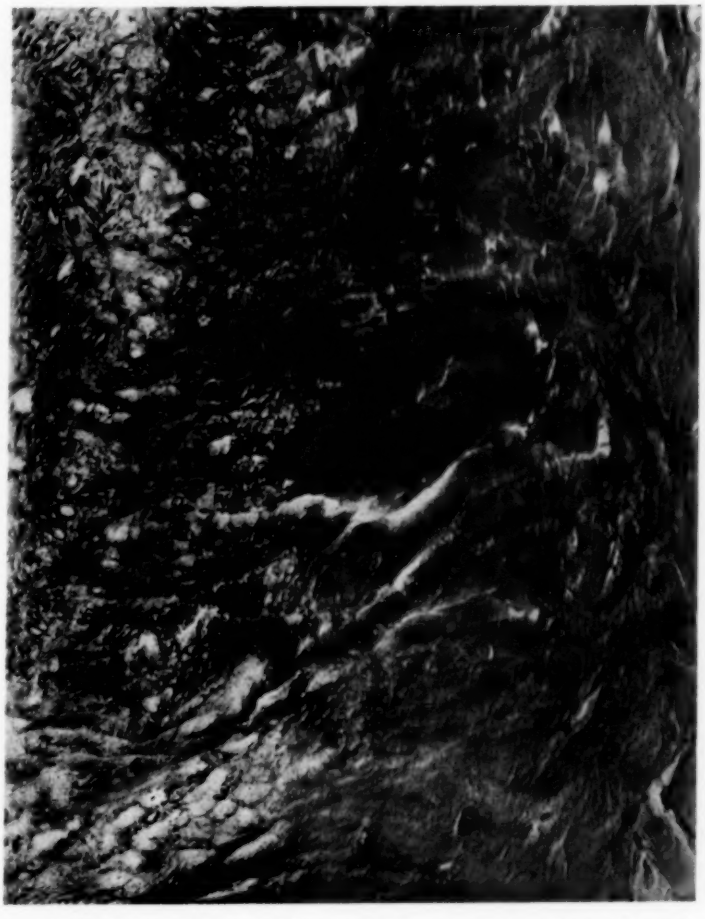

FIG. 5. Group I B. Male, aged 66. Calcareous nodule at base of aortic cusp showing slight cellular infiltration nearby. (× 100.)

least evidence of inflammation in the myocardium and most evidence of atherosclerosis with involvement of the coronary vessels.

From the evidence gathered in this study then, one must conclude that sclerosis of the aortic valve, with varying degrees of calcification and stenosis, in those cases without obvious etiology, such as syphilis or rheumatic fever, is not on an infectious basis but rather on the same basis as atherosclerosis.

It is not unreasonable to draw an analogy between the aortic valve and the aorta. In the latter we frequently find extensive calcium deposits and no evidence of any foregoing infectious process. We explain this as a "metabolic" disturbance and if we find cellular infiltrations about the calcareous nodules we consider them secondary. If, on the other hand, there is evidence of an old syphilitic aortitis we may make a diagnosis of aortic atherosclerosis on a syphilitic basis. Thus also with the aortic valve, it may be concluded that the final picture of aortic endocardial sclerosis with calcification and stenosis can be produced either by a chronic inflammatory process or a metabolic disturbance. The evidence in this series, however, indicates that in those cases having obscure etiology and showing other characteristics in common with the group presented by Christian,[5, 6] the condition develops upon a noninfectious basis.

Summary

1. Fifty-two cases were selected from 4,000 consecutive autopsies for the purpose of studying calcareous aortic valvular disease.

2. These cases were divided into four main groups, the first having two subdivisions:

Group I A: Ten cases showing calcareous aortic valvular disease with varying degrees of stenosis, undetermined etiology and no other important valvular alterations.

Group I B: Nineteen cases showing calcareous aortic valvular disease with significant changes in other valves.

Group II: Nine cases showing calcareous aortic valvular disease with known syphilitic etiology.

Group III: Eleven cases showing lesions of the aortic valve of known rheumatic fever origin.

Group IV: Three cases showing active aortic valvulitis of nonsyphilitic and nonrheumatic origin.

3. The clinical and pathological findings in these groups of patients have been presented, analyzed and compared.

4. Certain conclusions have been drawn from this study:

a. There is no proof that the etiology of aortic stenosis of the type seen in group I A lies among the infectious diseases, since none of these diseases specifically characterizes this group.

b. Microscopical studies indicate that stenosing calcareous aortic valvular disease in those cases without obvious cause, such as syphilis or rheumatic fever, is usually on a noninflammatory basis.

c. Unless the stenosis be fairly well marked, calcareous aortic valvular disease may not be diagnosed on physical signs without the aid of the roentgenogram.

d. The end result of a chronic aortic valvulitis may not be distinguishable from that of the noninflammatory calcareous lesion.

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THE TREATMENT OF CHRONIC INTRACTABLE ASTHMA WITH POLLEN EXTRACTS*

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Most clinicians are in agreement that pollen is the most important cause of asthma (Duke,[1] Walzer,[2] Vaughan[3]). While there are many ardent advocates of measures to combat factors other than pollen—especially food, bacterial infections, house dust, and physical allergy—relatively little stress has been laid on the treatment of chronic asthma due to pollen.

The obvious reason for this is, of course, the difficulty of recognizing the apparent paradox that in a patient who has been wheezing continuously throughout many years, the asthmatic condition may have originated from seasonal pollen asthma or pollen hay fever. Furthermore, in the chronic asthmatic, skin tests are frequently of limited value, a fact which adds greatly to the diagnostic difficulties. Negative tests are often encountered in the face of definite sensitivity (Peshkin[4]). On the other hand, if in this type of asthmatic treatment is instituted, frequently such marked sensitivity may be encountered that even the smallest dose of pollen extract produces a great aggravation of the symptoms and therefore discourages the patient and the doctor from further pollen injections.

An additional reason for the lack of enthusiasm concerning this treatment is this: whereas there have been many effective measures, such as the elimination of foods and of epidermals, etc., which were available for combatting asthma due to substances other than pollen, until recent years pollen treatment had not been sufficiently perfected to be successful in the treatment of the more severe types of hay fever and particularly of asthma. Three distinct advances in regard to this treatment can be recorded as being of relatively recent date: first, the surveying and charting of the air content of pollen in various cities, initiated and fostered by O. C. Durham; secondly, the realization of the fact that some patients need considerably larger doses than those formerly given; thirdly, the introduction of perennial pollen treatment by A. Brown,[5] and its further elaboration by Figley,[6] Vaughan,[7] and others.

Rôle of Pollen in Perennial Asthma

In looking over the skin test records of 121 consecutive patients with chronic asthma of the perennial type, it was found that there were more positive skin reactions to pollen than to any other group of allergens. (Table 1.) Among the 121 patients, in 65 the approximate date of the first onset of asthma could be definitely determined from the history. The analysis showed that in 63 per cent the first attacks started between August 15 and September 30, the ragweed season; in 20 per cent, during June and July;

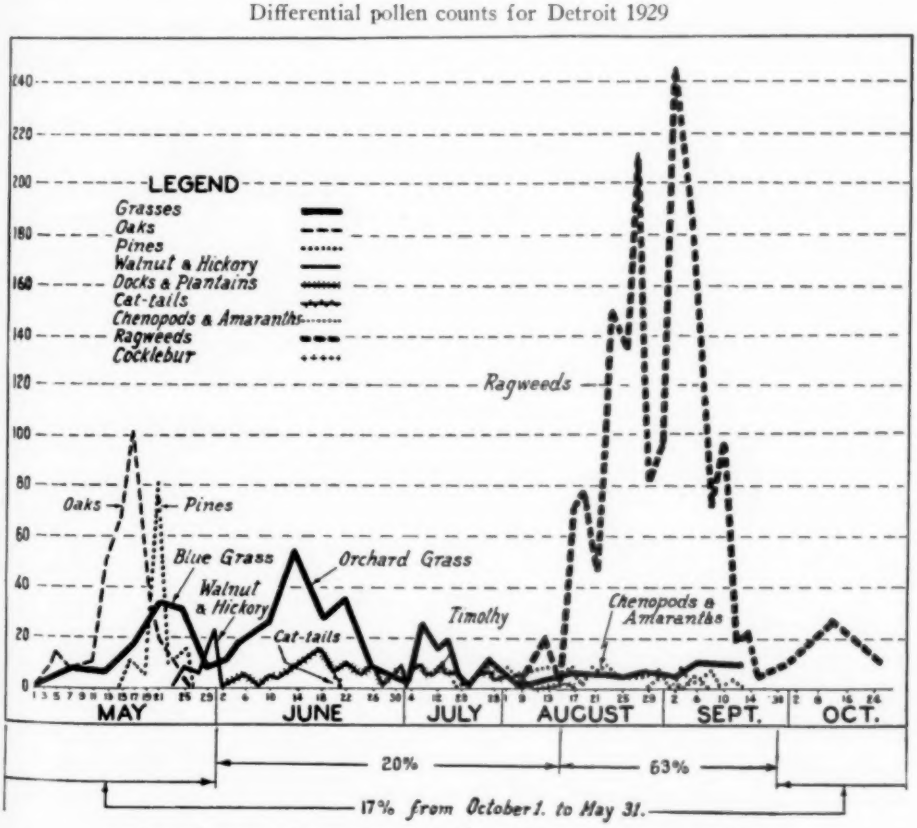
* Read at the Montreal Meeting of the American College of Physicians, February 9, 1933.

TABLE I
Comparison of Positive * Pollen Reactions with Those of Epidermals and Foods in 121 Cases

	Epidermals	Food	Pollen
Positive skin tests (exclusive of bacteria, fungi, dusts, and "incidentals")	483	1699	1330
Or in proportion (pollen—1)	0.36	1.28	1
Number of routine tests in each case	16	148	42
Or in proportion (pollen—1)	0.38	3.52	1
Positive skin tests if number of tests for each group were equal	1267	482	1330

* Including dermal, intradermal, "borderline," late reactions and repeated testing.

while in only 17 per cent did the first attacks of asthma occur during other months. If we check these data with the approximate time of pollen peaks in Detroit, we can well appreciate the rôle which pollen plays in the production of chronic asthma. (Figure 1.) This is corroborated further by the



Date of onset of first attack in 65 patients with chronic asthma

FIG. 1. Periods of onset of asthma as compared to periods of pollen incidence.

fact that the largest number of asthma sufferers in this locality present themselves for treatment during or shortly after these peaks, namely in July, September and October.

The rôle of pollen in the production of asthma is somewhat at variance with that of other substances. It is apparent that other antigens can be eliminated from our surroundings with much less difficulty than pollen. If a spontaneous desensitization to food or other antigens is possible through continuous exposure, this mechanism of recovery is entirely out of the question with pollen because of its periodic appearance and disappearance from the air. Moreover, in pollen allergy there is, during the season, a continuous absorption of antigen throughout day and night which is again in contrast with the mode of absorption with most other allergens—particularly food. All these factors make the case of severe pollen asthma much more refractory to therapy than other types of "extrinsic" asthma.

"Post-Pollen" Asthma

Before further enlarging on this subject it is necessary to draw attention to a definite type of asthma which, although unsatisfactorily explained at present, seems to be very pertinent to the question of pollen sensitization. In my experience with asthma, the most persistent resistance to treatment is encountered during the months of October and November. I have made several attempts to investigate this phenomenon. In 1929 to 1930, I tested 25 patients with various leaf extracts assuming some relationship of the falling and disintegration of the leaves to this type of asthma. While in one case (M. G.) a definite reaction to a chestnut leaf was obtained, desensitization in the following year proved to be a failure. I further attempted to culture molds and fungi from these leaves, checking the organisms obtained with those found in the sputum of patients. Several distinct skin reactions were observed; in treating one patient (W. M.) with mold extracts, I encountered a definite constitutional reaction which pointed to an etiological connection. On the whole, however, the data were inconclusive.

I have noted repeatedly that patients with seasonal pollen asthma, without marked additional sensitization, when living in pollen-free rooms may present symptoms for from two to three weeks after the disappearance of pollen from their surroundings. If one considers that during the end of the ragweed season many are subject to development of sensitization to cold and to bacterial or fungi infection, it is rather apparent that infection of the nasal and bronchial mucosa with bacteria and molds may play a large part in the continuation and aggravation of the seizures and in addition may give rise to other secondary sensitizations, such as to epidermals, dusts and foods. In other words, it appears that chronic asthma very often starts with a primary pollen sensitization which then becomes aggravated by infections and continues through the production of secondary sensitizations of other types.

Method of Treatment

Of the series of 121 consecutive patients with perennial asthma, 26 were selected who were of the most severe type and had been under continuous care for at least 12 months. Their asthma had been continuous, with an average duration of six and one-half years. Some of these cases were in extremis when first seen. They all had had previous treatment for asthma either by myself or other physicians, particularly by the use of elimination diets, vaccine-therapy, roentgen-ray treatment, nasal operations, and drugs, especially iodides and stramonium. Most of these patients were chronic users of epinephrine, opiates, and ephedrine.

Close questioning revealed the fact that in 10 there was no variation of symptoms throughout the year, while in the 16 there were definite exacerbations of symptoms during the months indicated in figure 2. This chart

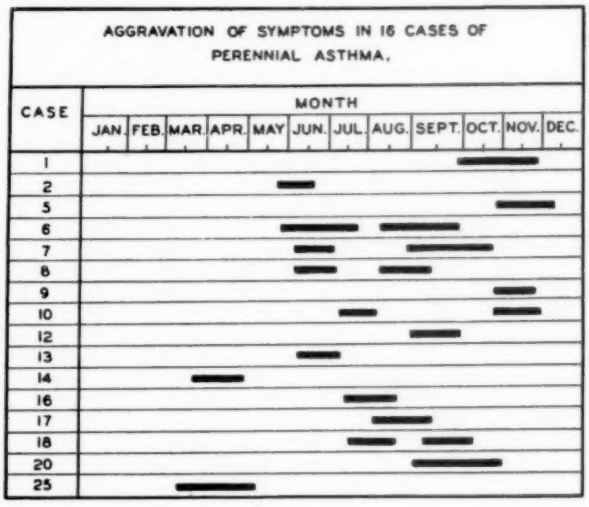


Fig. 2

again indicates the relationship of chronic asthma with the pollen content of the air. In 11, scratch tests were negative when the patients first came under my observation. On repetition of the tests, and substitution of the scratch method by intradermal, conjunctival and passive transfer tests, all but two patients were found to react positively to pollen. The pollen injections were given in the same manner as in hay fever patients. Treatment was started at any time of the year, namely as soon as the patients came under my care. The patients received a mixture of short and long ragweed, timothy, June grass, and orchard grass, together with such other pollens as were indicated by their history and skin tests. English plantain and some of the tree pollen were frequently used. In those in which skin tests and history gave no clue as to treatment, all the above pollens were included. An attempt was made to reach the maximum dose of the pollens at the beginnings of their respective seasons.

The dose employed is, I believe, a very important factor in successful treatment. When the patient presented himself during the pollen season, very small amounts of pollen extracts were used at frequent intervals, adjusting the dose cautiously by watching for the appearance of local reactions and general response to treatment. In treatment during the season the objective was to obtain a small wheal rather than to reach a large final dose.

In preseasonal treatment the doses were considerably higher than during the hay fever season, ranging on an average between ten to thirty thousand units. Some of the patients received as a maximum dose 3 c.c. of the 2.5 per cent extract (75,000 units) of each pollen. When the larger doses were given it was sometimes necessary to inject the extract of one pollen on one day and that of the other on the next in order not to produce too much local swelling. In a few cases it was necessary to direct treatment towards factors other than pollen, particularly within the first weeks after the patient presented himself for treatment. However, no other form of therapy was carried on systematically for any length of time. An effort was made to record such additional measures in table 2.

Reactions

The impression has been previously recorded[8] that patients with chronic asthma do not as a rule present the typical anaphylactic reaction following a pollen injection. In this series of cases this was again demonstrated. Patients whose doses were not correctly adjusted developed merely an increase in their asthmatic manifestations, usually within one-half to three hours, instead of the customary reaction of urticaria, sneezing, cough, etc.

Accordingly, care has to be exercised to increase dosage cautiously and to avoid the accident of an intravenous injection. In treatment during the season especial caution should be used. It has been observed on several occasions that treatment with ragweed extracts was greatly hampered during the peaks of the spring pollen season, because of the great susceptibility of the patient to reactions, probably due to absorption of both pollens.

Considering all of these factors, most of which have been outlined before, I merely wish to stress the fact that an aggravation of symptoms by the injections should always be regarded as an indication that the pollen administered will finally be effective, but that its dose should be gauged more cautiously.

Results

During an average time of observation of 23.4 months, of 26 cases treated (table 4) six were entirely free from attacks, nine had one or two minor attacks during the year, seven were improved but are still wheezing occasionally, four had no relief whatsoever. In some cases the results were spectacular. For instance, Case 21 had taken 20 to 30 c.c. of epinephrine daily before he came under my care, resulting in large abscesses on both arms. Case 20 had been greatly emaciated and despondent. In both in-

TABLE II

No.	Age	Sex	Years of Asthma	Name	Began Treatment On **	Results *	Skin Reactions to Pollen		Remarks
							On First Testing	Repeated † Tests	
1	15	M	9	B. C.	7–2–29	++ Entirely free from asthma.	Pos.		No more treatment since Oct. 1931.
2	14	F	12	A. M.	3–5–31	++ Entirely free since June 1931.	Pos.		
3	66	F	8	M. K.	2–12–31	+ One attack in Jan. 1932 due to shrimps; otherwise no asthma.	Neg.	Pos. (I)	
4	49	F	9	F. G.	9–15–31	− No relief.	Neg.	Pos. (I)	House dust injections relieved.
5	11	M	4	R. E.	1–30–31	+ Two attacks Feb. and Nov. 1931; otherwise free.	Pos.		
6	55	F	9	H. U.	3–12–31	+ Free except for one slight attack, tree season, 1932.	Neg.	Pos. (D)	
7	8	M	4	W. M.	10–3–31	+ Much relieved but slight recurrence July 1932 and Nov. 1931.	Pos.		Had four injections of yeast extract.
8	41	M	20	F. M.	12–1–30	+ Slight wheezing in Dec. 1930; otherwise free.	Pos.		
9	26	M	8	H. R.	9–18–29	++ Nasal catarrh Nov. 1931; otherwise completely free.	Neg.	Pos. (D)	Temporary food elimination.
10	50	F	3	W. C.	6–22–31	+ Considerable relief but still an occasional attack (infectious).	Neg.	Neg. (DICP)	Received autogenous vaccine recently.
11	48	F	9	G. L.	5–27–31	+ Much improved since Feb. 1932 but not free.	Pos.		

* ++ Excellent
+ Good or fair } Results.
− No

** Under observation until January 1933.

† (D) Dermal, (I) Intradermal, (C) Conjunctival, (P) Passive transfer.

TABLE II (*Continued*)

No.	Age	Sex	Years of Asthma	Name	Began Treatment On **	Results *	Skin Reactions to Pollen		Remarks
							On First Testing	Repeated † Tests	
12	22	M	9	R. B.	1–8–28	+ Slight attack in July 1932; otherwise free.	Pos.		
13	36	F	6	R. L.	9–18–31	+ Slight attacks but much improved.	Pos.		Sensitive to numerous allergens.
14	55	M	8	J. C.	6–13–31	− No relief whatsoever.	Neg.	Neg. (DI)	Expired following pneumonia.
15	43	F	6	L. B.	9–17–31	+ Much relieved but slight recurrences at height of timothy and ragweed seasons.	Neg.	Pos. (I)	
16	46	M	20	W. H.	5–21–31	+ Entirely free but recurrence at timothy and ragweed seasons 1932.	Neg.	Pos. (I)	Attacks readily controlled by daily injections.
17	11	F	7	J. F.	1–22–31	+ Three slight attacks in 1932; otherwise completely free.	Pos.		Recent attacks due to peanuts.
18	8	M	5	V. P.	5–10–30	− No improvement.	Pos.		
19	15	F	5	M. S.	2–22–30	++ Completely free.	Pos.		
20	13	F	7	E. G.	9–24–30	+ Bronchitis in June; slight wheezing on Sept. 4, 1932; otherwise completely free.	Pos.		
21	42	M	4	R. D.	5–5–31	+ Well for 15 mos.; discontinued treatment; relapse during ragweed season 1932.	Neg.	Pos. (C)	Had taken 30 c.c. epinephrine daily before under my care.
22	47	M	4	A. W.	12–9–31	+ Some relief but attacks still persistent.	Neg.	Pos. (D)	
23	12	M	4	M. F.	1–2–31	− No relief.	Neg.	Pos. (I)	Living near chicken coop; strong reaction to chicken feathers.
24	14	F	12	B. M.	6–4–31	++ Free from asthma.	Pos.		
25	45	F	3	L. S.	9–10–31	+ Little response at first; much improved since April 1932.	Pos.		
26	11	M	4	J. V.	11–15–31	++ Free from asthma.	Pos.		

stances, two small injections of pollen extract initiated immediate relief which lasted for more than 14 months. It is interesting to observe that most of those patients who did not recover completely had recurrences at the height of the pollen seasons. This probably indicates that either an insufficient dose had been given or that the wrong selection of pollens had been made. I do not feel that an overdose accounted for the existence of symptoms, because in most instances further increase of the dose controlled the existing symptoms. Some of the failures are unquestionably due to insufficient attention to other sensitizations. For instance, Case 3 had been free from asthma until one day when she fried and ate oysters which produced an immediate attack of asthma. The greatest resistance to treatment was encountered during the "post-pollen season." In some of the patients who started treatment at this time, several weeks elapsed before the beneficial effect could be noted. As table 3 indicates, those patients who gave positive skin tests responded more readily to treatment than those in whom the testing was negative.

TABLE III

Results According to Skin Reactions to Pollen

Number of Cases	Excellent	Good and Fair	No improvement	Total
Pollen-sensitive on first testing (dermal)....	6	7	1	14
Positive on check by dermal, intradermal, conjunctival, and passive transfer tests...	2	6	2	10
Negative.....		1	1	2
Total.....	8	14	4	26

DISCUSSION

In explaining the results obtained, one could well assume a nonspecific effect of the pollen extract. However, the following considerations weigh against this viewpoint. All patients in this series were sensitive to more than one group of antigens. It is well known that the control of one of the main offensive substances such as a certain food or animal emanation may bring about a marvelous recovery, in spite of the fact that some of the remaining allergens are still at work. Vaughan has noticed that in pollen-sensitive individuals perennial treatment appeared to free the patients from attacks due to other sensitizations. In accord with this experience and with the evidence set forth that pollen can be considered as the most common offender in most cases, we can well expect that the control of the pollen factor will be equally as, if not more successful than the control of any other allergens. With this in mind we can explain the improvement during the winter months when no pollen is in the air. Undoubtedly the prevention of nasal infection during the pollen months tends to counteract the development of secondary factors, particularly infection.

The advocacy of this treatment should not induce us to neglect the value of other measures for the relief of this type of case. In fact, some of the patients recorded here were subsequently further relieved by control of other factors. Comparison, however, of the results of perennial pollen treatment with those obtained by vaccine treatment (Rackemann [9]), food elimination (Rowe [10]), and other measures seem to me to warrant that attention to pollen sensitivity be given foremost consideration.

Conclusions

1. Among 121 cases with chronic perennial asthma, it was found that pollen played the most important part as a causative factor. This was evidenced by a distinct aggravation of symptoms during the pollen peaks, by the history of onset of the first attacks during the time of pollination, and by comparison of the results of the skin tests.

2. Attention is directed to the frequent aggravation of asthma shortly after the pollen season ("post-pollen asthma"). A proper explanation for this type of asthma cannot be given at present.

3. Of the 121 cases, 26 were selected because they presented unusually severe asthma and had been under continuous observation for at least 14 months. Injections with a combination of the extracts of the most important hay fever pollens of this area were given. The results obtained compare favorably with those of any other measure devised so far for treatment of this type of case.

4. Among the 26 patients, the initial tests for pollen by the dermal method were negative in 11. In all but two patients positive tests were obtained by repeated testing subsequently. The therapeutic results were decidedly better in those who gave positive tests at the first testing.

5. In administrating pollen extract to asthmatics, attention should be directed to the following points: (1) The maximum dose, as a rule, should be higher than for hay fever patients; (2) Aggravation of the symptoms following injections should be regarded as an indication that the treatment finally is likely to prove successful, but that an overdose has been given; (3) During the height of the pollen season, treatment should be given with the proper precautions recently outlined by others for co-seasonal treatment.

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RENAL GLYCOSURIA*

By A. F. Fowler, M.D., C.M., *Montreal, Canada*

In 1931, within a few days, two children were admitted to the children's ward of The Montreal General Hospital with glycosuria. One was a girl, the other a boy. Their ages were four and one-half and five years respectively. In each case the urine, in addition to sugar, contained acetone. The girl had renal glycosuria and the boy was suffering from acute diabetes with severe acidosis (precoma). To have assumed that the girl was a diabetic suffering from acidosis because of the glycosuria and acetonuria, and to have given her insulin without certain precautions, would, to say the least, have endangered her life; whereas, in the case of the boy, insulin treatment was imperative. The purpose of this communication, therefore, is to deal with the general management of such cases. This case of renal glycosuria is also reported because of the age of the child and the opportunity afforded to deal with the problem of renal glycosuria.

Case Report

The child, a white female four and one-half years of age, was admitted to the hospital on May 22, 1931 with a history of vomiting, lassitude, loss of weight, loss of appetite and headache.

The family history was irrelevant; there was no history of diabetes or of glycosuria. The child's past history was also irrelevant; she was born at full term, was breast fed for eight months and the only illness was measles at the age of three years.

The present illness, vomiting, etc., appears to have dated back seven weeks prior to admission to the hospital, the prominent features being periodic attacks of nausea and vomiting. During these attacks the child would refuse food and was kept in bed.

The physical findings were negative except for slight fever (T = 99.2), drowsiness, undernutrition (weight 28 pounds), an injected pharynx and acetone odor to the breath. The laboratory data were as follows:

Urine: Acid reaction; S.G.—1030; sugar plus; acetone plus; no albumin; microscopic findings, negative.

Blood:	Red cells	3,790,000
	White	11,150
	Sugar	0.101 per cent
	Urea-N	24 mg. per 100 c.c.
	Cholesterol	0.119 " "
	Wassermann	Negative.

Additional Data:

Tuberculin Test: 1/10 c.c. 1/1000 O.T., negative; 1/10 c.c. 1/100 O.T., negative.

* Read before the Seventeenth Annual Clinical Session of The American College of Physicians, February 8, 1933.

From the Department of Metabolism, The Montreal General Hospital.

X-Rays—*Chest*—Negative, except for moderate and generalized increase of bronchial and peri-bronchial thickening.

Sella Turcica—Rather small. No destruction of floor or of clinoid processes.

Feet—Epiphyses normal.

The combination of glycosuria, acetonuria, drowsiness, leukocytosis and increase of blood urea nitrogen suggested diabetes with acidosis. Opposed to diabetes there was the normal blood sugar and opposed to severe acidosis of diabetes was the absence of albuminuria. As is well known, albumin and a shower of casts in the urine is an almost invariable finding in the diabetic approaching coma. The impression, therefore, was that the child was suffering from some gastrointestinal upset, commonly met with in childhood, and that the fever and leukocytosis were the result of the latter or due to the injected pharynx. The child was, therefore, given the usual ward diet for her age—a diet liberal with respect to carbohydrate. The following day, the urine, though it contained sugar, was free of acetone and the blood sugar, obtained in the fasting state, was again normal.

The subsequent clinical history is irrelevant except for the glycosuria. The acetonuria on admission was regarded as a starvation phenomenon, as it disappeared following the institution of a liberal carbohydrate diet without the aid of insulin. Since the glycosuria persisted and appeared to bear no relationship to the clinical picture, renal glycosuria was suspected. The child was, therefore, subjected to the routine examination of such cases in this Clinic, as previously described by Rabinowitch.[1]

A diet was prescribed containing definite quantities of carbohydrate, fat and protein. The carbohydrate content was then gradually increased and blood and urine sugar estimations were made daily. The combined data obtained between May 30 and June 9 are recorded in table 1. The following will be noted.

(*a*) Glycosuria was *constant*. This is shown in the periodic examinations throughout the day. Samples were collected as follows: 8 a.m. to 12 noon; 12 noon to 5 p.m.; 5 p.m. to 10 p.m.; 10 p.m. to 7 a.m.; and 7 a.m. to 8 a.m. The purpose of this method of sampling was to determine separately the effects of breakfast, the noon and evening meals, and the metabolism during the night and that in the fasting state.

It may here be observed that the sugar was identified as glucose.

(*b*) The amount of sugar excreted was small, ranging between 1.9 and 7.4 grams per 24 hours. A possible source of error must be considered here in that the collection of urine was not quantitative; some was lost. It will, however, be noted that for corresponding volumes of urine the total amounts of sugar were approximately the same regardless of the carbohydrate content of the diet.

(*c*) There was no relationship between the intake and ouput of sugar; the urine contained no more sugar when the diet contained 300 grams of carbohydrate than when the intake was 150 grams.

(*d*) The blood sugars were *always* normal in the fasting state.

(*e*) Acetone was found in the urine during the first three days of observation only. It disappeared with the disappearance of the vomiting and starvation.

On June 9, as it was considered that the child had acquired a reasonably good store of glycogen, a blood sugar time curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.100 per cent. Twenty-five grams of glucose were then given by mouth with the following results:

Time	Blood sugar (per cent)
30 minutes after ingestion	0.125
60 " " "	0.156
120 " " "	0.091
150 " " "	0.100

TABLE I

Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar					Glycosuria * (periodic)					Blood Sugar (per cent)	Diet			Remarks
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a.m. to 12 noon	12 noon to 5 p.m.	5 p.m. to 10 p.m.	10 p.m. to 7 a.m.	7 a.m. to 8 a.m.		Carbohydrate	Fat	Protein	
May 30	115	2.5	2.7	+	0	+	+	+	tr.	+	0.086	150	53	56	25 c.c. 40% glucose every two hours for 5 doses.
31	170	1.3	2.2	+	0	+	+	+	+	+	0.101	200	53	56	" " " " " "
June 1	195	2.7	5.3	+	0	+	+	+	+	+	0.122	250	53	56	" " " hour for 10 doses.
2	155	3.8	5.9	0	0	+	−	+	+	+	0.111	300	53	56	" " " " 15 "
3	75	6.2	4.6	0	0	+	+	+	+	tr.	0.105	300	53	56	" " " " " "
4	130	5.0	6.5	0	0	+	+	+	+	tr.	0.120	300	53	56	" " " " " "
5	180	4.1	7.4	0	0	+	+	+	+	tr.	0.101	300	53	56	" " " " " "
6	230	1.3	3.0	0	0	+	+	+	tr.	tr.	0.113	300	53	56	" " " " " "
7	75	2.5	1.9	0	0	+	+	−	+	+	0.084	300	53	56	" " " " " "
8	150	3.5	5.2	0	0	+	+	−	tr.	−	0.116	300	53	56	" " " " " "
9	105	4.1	4.3	0	0	+	+	+	tr.	−	0.100				Blood sugar time curve.

* Minus signs indicate no specimen obtained.

The urine was collected at the above periods and sugar was found in all specimens.

In view of the above findings a full hospital diet was prescribed and the child was kept under observation until July 13. During this time the urine *always* contained sugar and the amount never exceeded 10 grams per 24 hours. There was no acetone or diacetic acid. The blood sugars were always normal in the fasting state.

On July 10, one month after the previous blood sugar time curve, another curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.088 per cent. Twenty-five grams of glucose were then given by mouth with the following results:

Time	Blood sugar (per cent)
30 minutes after ingestion	0.113
60 " " "	0.133
120 " " "	0.106
150 " " "	0.087

The urine was collected at the above periods and sugar was again found in every specimen.

Because the child failed to coöperate, data with respect to the respiratory metabolism were not obtained. In view, however, of the clinical course and the laboratory data a tentative diagnosis of renal glycosuria was made and the child was discharged from the hospital on July 14. The mother was instructed to bring her to the Clinic for Diabetes for observation periodically.

The child was not seen or heard of again until March 1932—eight months later. The reason given by the mother for her failure to follow instructions was that the child was well. During the interval, there were no restrictions whatever with respect to her diet. She was again admitted to the hospital for observation.

On admission, it is of interest to note that the urine, in addition to sugar, again contained acetone. This was a starvation phenomenon; the child, on learning that she was to be admitted, had refused most of her food for three days.

The observations made were practically identical with those of the former admission and with practically identical results. The combined data are shown in table 2. It will be noted firstly, that following ingestion of liberal quantities of carbohydrate the acetone again disappeared shortly after admission; secondly, that there was constant glycosuria; thirdly, that there was no relationship between the intake and output of sugar; and lastly that all blood sugars, in the fasting state, were again normal. A blood sugar time curve was obtained on April 2, 1932 with the following results:

In the fasting state the blood sugar was normal, namely, 0.089 per cent. Twenty-five grams of glucose were then given by mouth.

Time	Blood sugar (per cent)
30 minutes after ingestion	0.133
60 " " "	0.119
120 " " "	0.100
150 " " "	0.082

The child was discharged on April 2, 1932 and was not heard of until January 17, 1933 when she was brought to the Clinic by her mother. A specimen of urine then showed sugar but no acetone. She was again recommended for admission. On learning that she was to be admitted the child again refused food and on admission, the following day, the urine, in addition to sugar, again contained acetone. The data obtained during this admission were essentially similar to those of the two previous admissions. The combined results are shown in table 3. This time, however,

TABLE II

Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar					Glycosuria * (periodic)					Blood Sugar (per cent)	Diet			Remarks
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a.m. to 12 noon	12 noon to 5 p.m.	5 p.m. to 10 p.m.	10 p.m. to 7 a.m.	7 a.m. to 8 a.m.		Carbohydrate	Fat	Protein	
March 23	315	1.2	3.7	+	0	+	+	+	tr.	tr.	0.052	150	50	56	
25	590	0.5	2.9	+	0	tr.	tr.	tr.	tr.	tr.	0.079	150	50	56	
26	250	0.9	2.2	+	0	+	+	+	+	+	0.095	150	50	56	
27	190	0.9	1.7	+	0	tr.	+	+	tr.	tr.		150	50	56	
28	282	2.1	5.9	+	0	+	+	tr.	tr.	tr.	0.111	150	50	56	
29	200	3.3	6.6	tr.	0	+	+	+	tr.	+	0.108	200	50	56	25 c.c. 40% glucose every two hours for 5 doses.
30	130	4.4	5.7	0	0	+	+	+	+	tr.	0.108	250	50	56	" " " " " hour for 10 doses.
31	150	3.3	4.9	0	0	+	+	+	+	+	0.095	300	50	56	" " " " " " " 15 "
April 1	150	3.8	5.7	0	0	+	+	+	+	+	0.091	300	50	56	" " " " " " " " " "
2	239	2.3	5.5	0	0	+	+	+	−	−	0.089				Blood sugar time curve.

* Minus signs indicate no specimen obtained.

TABLE III

Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar					Glycosuria (periodic)					*Blood Sugar* (per cent)	Diet			Remarks
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a.m. to 12 noon	12 noon to 5 p.m.	5 p.m. to 10 p.m.	10 p.m. to 7 a.m.	7 a.m. to 8 a.m.		Carbohydrate	Fat	Protein	
Jan. 19	460	2.1	9.7	++	0	++	++	++	++	++	0.111	150	50	56	
20	812	2.1	17.0	++	0	++	++	++	++	++	0.069	200	50	56	25 c.c. 40% glucose every two hours for 5 doses.
21	545	3.1	16.9	++	0	++	++	++	++	++	0.111	250	50	56	" " " " " hour for 10 doses.
22	689	5.0	34.4	tr.	0	++	++	++	++	++	0.113	300	50	56	" " " " " " " 15 "
23	472	5.0	23.6	0	0	++	++	++	++	++	0.097	300	50	56	" " " " " " " " "
24	450	3.3	14.8	0	0	+	+	+	+	+	0.091				Blood sugar time curve.

throughout the period of observation the child had fever of unknown origin, the temperature ranging between 99° and 100° F. The child refused most of her food during the first few days and on one occasion the urine showed sugar, acetone and diacetic acid. Following liberal diet with glucose feedings the acetone disappeared. Again, glycosuria was constant and the amounts of sugar excreted daily were small. All blood sugars were again normal in the fasting state and on January 24, 1933 a blood sugar time curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.093 per cent. Twenty-five grams of glucose were then given by mouth.

Time	Blood sugar (per cent)
30 minutes after ingestion	0.143
60 " " "	0.158
120 " " "	0.109
150 " " "	0.109

Summary of Case

To summarize, we have here a child who, when first seen, was four and one-half years of age and is now six years old; and who has had constant glycosuria as shown by 198 analyses. The sugar has been identified as glucose. The amounts excreted have been always small and not related to the carbohydrate content of the diet. The blood sugars, in the fasting state, have always been normal. In all there have been 33 analyses. Four blood sugar time curves obtained at long intervals of time have been normal. There have been no clinical signs or symptoms to suggest diabetes other than at the first admission to the hospital. At that time, these were readily explained by a gastrointestinal disturbance and injection of the pharynx.

That the acetonuria on each admission was due to the starvation and not to diabetes is suggested from the fact that it disappeared following the administration of food *without* insulin. The best indication, however, of the absence of diabetes is the fact that the child has been on an unrestricted diet for over one and one-half years and is well. As is well known, in juvenile diabetes when in addition to glycosuria the diabetes has reached the stage of ketosis and acidosis, death is the rule within a very short time, unless insulin is administered.

Discussion

As has been repeatedly emphasized in this Clinic and will again be shown, *renal glycosuria is rare.* Cases in which, in addition to sugar, acetone is found in the urine are still more rare; and, as demonstrated in the case just reported, they present difficulties in diagnosis. In renal glycosuria, *acetonuria* is merely a starvation phenomenon and is usually due to persistence in the attempt to free the urine of sugar by restriction of diet or, as in our case, to vomiting and its resultant starvation. Children, as is well known, are particularly susceptible to ketosis. This case, therefore, emphasizes the fact that absence of ketosis is not a necessary criterion for the diagnosis of renal glycosuria. This is contrary to the view still expressed as late as 1931 by Peters and Van Slyke.[2] Much more important diagnostically than the absence of ketosis is the finding of *constant* glycosuria for, as will presently be shown, with this criterion many cases of so-called renal glycosuria recorded in the literature are excluded.

Incidence

In approximately 4000 cases of glycosuria investigated in the Clinic for Diabetes of this hospital 13 individuals only were ever regarded as renal glycosurics. Six of these cases are, however, now excluded because the conditions do not conform to all of the necessary requirements for such diagnosis. We are, therefore, left with seven cases only —an incidence of 1.75 per 1000 glycosurics. In the fourth edition of "The Treatment of Diabetes Mellitus" Joslin reported 47 cases of renal glycosuria in the first 6000 cases of glycosuria. In the next 3000 cases 19 more were so classified, making 66 in all. As a result, however, of a recent re-investigation of these cases by Marble,[3] one of Joslin's assistants, and the use of diagnostic criteria similar to those of our Clinic, the number of cases of typical renal glycosuria was reduced to 15. This gives an incidence of 1.66 per 1000, which, it will be observed, agrees very closely with our own. Combining the data of the two clinics, it will be observed that 22 cases only have been found among approximately 13,000 glycosurics. That many cases diagnosed as renal glycosuria eventually prove to be otherwise is shown by experience in this clinic. Six such individuals previously diagnosed as renal glycosuria elsewhere were subsequently admitted to this hospital with the signs of active diabetes. In two of these cases, at the time of admission, the patients were in precoma. In another case the individual had developed a cataract.

The youngest renal glycosuric recorded in the literature is that reported by Paullin and Bowcock.[4] Glycosuria was discovered when the child was two years old and it has been constant since. Goldbloom[5] reported a child 20 months old and Williams[6] a child three and one-half years of age. These last two cases are, however, excluded, according to our criteria, as in both it is stated that the urine subsequently became free of sugar.

Diagnostic Criteria

The diagnosis of renal glycosuria involves the use of laboratory procedures which as a rule are available only in hospitals. The safest rule for the physician in general practice is, therefore, to assume that every glycosuric is a diabetic until proved otherwise; as we have repeatedly emphasized, it is much safer to underfeed a normal individual than to overfeed a diabetic.

The criteria for the diagnosis of renal glycosuria are as follows:

1. Glycosuria must be *constant*.
2. The type of sugar found in the urine must be identified as glucose.
3. There must be little or no relationship between the intake and excretion of sugar.
4. There must be no clinical signs or symptoms of diabetes.
5. There should, ideally, be no family history of diabetes.

6. The blood sugar in the fasting state must always be normal.
7. The blood sugar time curve after the ingestion of glucose must be within normal limits.
8. The rate of utilization of sugar, as determined by the respiratory metabolism, must be normal.
9. The individual must not subsequently develop diabetes.

These conditions will now be considered in greater detail.

1. Glycosuria must be constant. It seems desirable, if renal glycosuria is to be regarded as a clinical entity, that this criterion should be insisted upon. Joslin agrees with this view, and in the 15 cases reported from his clinic and in the seven from this clinic, glycosuria was found constantly.

2. The type of sugar found in the urine must be identified as glucose. This requires no comment.

3. There must be little or no relationship between the intake and excretion of sugar. As the collection of urine in the child reported here was not strictly quantitative, the data of another case, an adult, are shown in table 4 to demonstrate this phenomenon.

TABLE IV

(Female; Age 22)

Date	Vol.	Urine		Blood	Diet			Remarks
		Sugar %	Sugar gm.	Sugar %	C.	F.	P.	
March 25	250	3.1	8	0.085	150	140	60	(Specimen of urine incomplete.)
" 26	900	2.5	22	0.111	250	140	60	25 c.c. 40% glucose q.1 h × 10 doses.
" 27	1050	3.3	35		350	140	60	50 " " " " " " "
" 28	1300	3.8	49	0.113	450	140	60	75 " " " " " " "
" 29	1050	3.5	37	0.109	450	140	60	" " " " " " " "
" 30	775	3.8	29	0.092	450	140	60	" " " " " " " "
" 31	650	3.3	21	0.095	450	140	60	" " " " " " " "
April 1...	650	4.1	27	0.120	450	140	60	" " " " " " " "
" 2...	1300	3.3	43	0.095	450	140	60	" " " " " " " "

It will be observed that though the carbohydrate content of the diet was increased 100 grams daily, the increase of sugar in the urine was relatively inappreciable. On a constant diet of 450 grams carbohydrate, 140 grams fat and 60 grams protein the sugar excretion in the urine varied from 49 to 21 grams in the 24 hours.

4. There must be no clinical signs or symptoms of diabetes. Signs of active diabetes help to exclude renal glycosuria, but *absence* of such signs are *alone* of very limited value, for they may also be absent in mild diabetes. There is an appreciable number of diabetics who present no clinical signs or symptoms other than the glycosuria, though the diabetes may be of long duration. In the clinic of this hospital, for example, there have been 71

individuals who had had the disease for 15 years or over. Of them 27 only required insulin. Of the remaining 44 individuals who did not require insulin, 16 had had the disease for 20 years or more. There were seven deaths in this group and in two instances at the time of death the individual required no insulin, the urines were free of sugar and there were no signs of active diabetes; death was due to other causes, such as cardio-vascular disease, etc.

As shown in the child reported here, the problem is not always simple. On admission to the hospital, the child had symptoms suggestive of diabetes, drowsiness, vomiting, leukocytosis, etc. Since renal glycosuria is rare, the safest rule, in general practice, when in doubt, is to administer sugar and insulin. Following such treatment the acetonuria usually disappears rapidly regardless of its cause, and insulin reactions are avoided because of the hyperglycemia induced by the administration of carbohydrates. After the drowsiness and acetone odor of the breath have disappeared and the urine is free of acetone, insulin may be discontinued and the effects of diet alone noted. If acetone reappears insulin and carbohydrate should again be administered simultaneously. When the acetone disappears permanently and diet is found to have no effect on the glycosuria and when the clinical condition is otherwise negative, renal glycosuria may then be suspected but should not be diagnosed in practice with limited laboratory facilities.

5. There should, ideally, be no family history of diabetes. This requires no comment.

6. The blood sugar in the fasting state must always be normal. There are cases in the literature in which the diagnosis of renal glycosuria was made largely because the blood sugar, when obtained in the fasting state, was normal. It might here, therefore, be observed that such blood sugars may be, and are commonly, found in early and mild diabetes, when the glycosuria is either transient or occurs after meals only (post-prandial glycosuria).

7. The blood sugar time curve after the ingestion of glucose should be within normal limits. There is general agreement as to the characteristics of a perfectly normal blood sugar time curve. The vagaries, however, are many and the following case is cited as an example.

A female, aged 22, was admitted to the hospital on March 18, 1932 with complaints referable to the gall-bladder and a tentative diagnosis of chronic cholecystitis was made. She was known to have had glycosuria prior to admission. There were no other signs or symptoms to suggest diabetes. A blood sugar time curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.083 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth.

Time	Blood sugar (per cent)	Urine sugar
30 minutes after ingestion	0.117	plus
60 " " "	0.192	"
120 " " "	0.200	"
150 " " "	0.166	"

The curve was abnormal; there was an abnormally high peak and at the end of two hours the blood sugar was still increased. On the day of the test, however, the patient had an upper respiratory infection with slight fever. This curve could also have been due to pancreatic disturbance secondary to the cholecystitis. The carbohydrate metabolism was then investigated as outlined above and is shown in table 4. It will be observed that no relationship was found between the intake and output of sugar. The diet of 450 grams carbohydrate, 140 grams fat and 60 grams protein was continued for 18 days, after which a second blood sugar time curve was obtained. During the interval the patient had slight febrile reactions on a number of days and also on the day of the test.

In the fasting state the blood sugar was normal, namely, 0.111 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth with the following results:

Time	Blood sugar (per cent)	Urine sugar
30 minutes after ingestion	0.153	plus
60 " " "	0.166	"
120 " " "	0.153	"
150 " " "	0.149	"

It will be observed that again there was evidence of disturbed carbohydrate metabolism. A cholecystectomy was subsequently performed and our Pathologist, Dr. L. J. Rhea, reported "chronic cholecystitis." For the following 10 months the patient was on an unrestricted diet. A third blood sugar time curve was then obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.091 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth.

Time	Blood sugar (per cent)	Urine sugar
30 minutes after ingestion	0.112	plus
60 " " "	0.125	"
120 " " "	0.131	"
150 " " "	0.111	"

It will be observed that the response to glucose ingestion was now perfectly normal. In this case the following additional points are of interest: (*a*) Every specimen of urine examined contained sugar—48 analyses in all; (*b*) the blood sugar in the fasting state was always normal—28 analyses in all; (*c*) the respiratory metabolism was normal; and (*d*) the disturbance noted in the blood sugar time curve disappeared with removal of the infected gall-bladder. The observations of Williams and Dick[7] are of interest here. These authors have recently demonstrated experimentally that decrease of carbohydrate tolerance may result from an acute infection; and that such loss of tolerance may be of some duration—several weeks or months. This finding agrees with the experience of this clinic.[8]

8. The rate of utilization of sugar, as determined by the respiratory metabolism, must be normal. Among the criteria for the diagnosis of renal glycosuria which are to be found in the literature the inclusion of this phenomenon is the exception rather than the rule. Finley and Rabinowitch[9] were the first to demonstrate this characteristic of renal glycosuria. Ladd and Richardson[10] subsequently confirmed these findings. Marble[3] agrees with Rabinowitch about the importance of this test but points out a possible fallacy in the interpretation of the data; mild diabetics may at times show

no impairment. The important fact, however, is that, while the diabetic *may* at times show a normal utilization of carbohydrate the renal glycosuric *must* show it.

9. The individual should not subsequently develop diabetes. A period of three years of observation from the time of the discovery of the glycosuria has been chosen arbitrarily by some workers as meeting the requirements of this diagnostic criterion.[3] The case reported here has, therefore, as yet to meet one of the requirements.

Summary

A case of renal glycosuria with ketosis in a child four and one-half years of age is reported. Difficulties in diagnosis and questions of treatment are considered. The importance of certain diagnostic criteria is discussed.

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EDITORIALS

PAROXYSMAL HYPERTENSION

THERE has existed for many years in the medical literature of foreign countries, and particularly in that of France, evidence of a keen interest among clinicians concerning those abrupt elevations of the systemic blood pressure to which the term paroxysmal hypertension has been applied. Elevations of the systolic blood pressure, often of over 100 mm. of mercury in the course of a relatively few minutes, are apt when they occur to produce striking subjective symptoms and to be accompanied by definite dangers. The etiology of such attacks, the mechanism by which they are produced, and the consequences that may ensue are all subjects which are worthy of the internist's attention.

Knowledge of the etiology of this syndrome, paroxysmal hypertension, is still at a stage when only certain clinical associations can be mentioned, without too definite claims as to cause and effect. In the first place, such abrupt rises in blood pressure have been not infrequently observed in a group of cases having in common the factor of a preëxisting unstable hypertensive state, i.e., in cases of acute glomerulo-nephritis, of eclampsia, of the malignant form of essential hypertension and in an occasional case of chronic lead poisoning. The abrupt rise in pressure in these instances often is accompanied by striking cerebral symptoms, such as violent headache, aphasia, amaurosis, and localized or general convulsive seizures. However, such phenomena probably more often appear at the end of a period of gradually rising pressure rather than in association with a sudden or paroxysmal rise.

It is of interest in this problem of the relationship of the cerebral symptoms to the blood pressure rise that in certain cases of focal cerebral lesions, tumor, internal hydrocephalus and old apoplectic softening, the occurrence has been noted of attacks beginning with a paroxysmal rise in pressure and eventuating in disturbances of consciousness or convulsive seizures. In this same general category should be placed the observations on the abrupt, but scarcely paroxysmal, rise in blood pressure which often accompanies a rapid increase of intracranial pressure due to concussion or to subdural or intraventricular hemorrhage. It has been observed also that occasionally lumbar puncture in disease of the central nervous system leads abruptly to a large temporary rise in blood pressure and the same phenomenon has been reported as an anomalous occurrence in connection with the administration of spinal anesthesia.

The mechanisms that underlie these associations of paroxysmal hypertension with disturbances in the central nervous system are still a matter of conjecture, but it would seem that the relationship is a highly significant one.

Attacks of paroxysmal hypertension occur even more frequently in a quite different clinical association, i.e., with disease of the coronary arteries and the aortic valves. The clinical physiognomy of the attacks in these instances is dominated by the effect upon the heart; of cerebral symptoms only throbbing headache is apt to be noted. The rise in blood pressure in these cases entails a sudden overload upon the left ventricle of a damaged heart. The myocardium may still be competent enough to meet the demand through the high pressure period, and if this is so only precordial distress and cardiac overaction are subjectively noted by the patient. The beginnings of acute incompetence of the left ventricle are accompanied, however, by some degree of anginal pain and by urgent dyspnea due to pulmonary congestion. If more complete failure of the ventricle follows, then pain subsides, dyspnea becomes intense and acute pulmonary edema may appear. At the same time the high blood pressure, which is itself dependent upon the effort of the left ventricle, falls slowly or abruptly. In the more seriously damaged hearts failure occurs before any great height of blood pressure is attained; initial pain may be lacking, dyspnea may be urgent from the start and pulmonary edema exhibit itself almost at once. A paroxysmal elevation of blood pressure, slight or great, depending upon the degree of cardiac competence, is the first event in the majority of those attacks which go labelled as angina with dyspnea, cardiac asthma, paroxysmal dyspnea, and acute pulmonary edema. In such cases in which the rise in pressure has been observed, when autopsy has been performed it has disclosed quite uniformly an advanced coronary sclerosis, very commonly with evidence of old cardiac infarction. Occasionally syphilitic coronary occlusion may be present. Entirely similar attacks have been reported in rheumatic aortic insufficiency but without postmortem data on the state of the coronaries. The cause of the attacks of paroxysmal hypertension in all these cases is still purely a matter for speculation.

There occur also moderately severe attacks of paroxysmal hypertension in patients, usually in the younger age periods, in whom no evidence of organic disease is present. Precordial distress, slight dyspnea and headache may accompany the rise in pressure but more serious sequelae are not observed. Disappearance of the attacks after a period of time seems usually to occur. A basis in the emotional life of the patient has been suggested but tangible evidence of such a disturbance is not always obtainable.

There is finally one type of paroxysmal hypertension in which the cause of the attacks is quite well known. A small number of cases have been reported in which sudden and violent rises in blood pressure have occurred as the result of the presence of a tumor of the medulla of the adrenal. In several of these cases the tumor has been removed operatively and the patient freed permanently of the attacks. These tumors are composed of chromaffine cells and have been shown to contain adrenalin in large amounts. The intermittent discharge of this adrenalin content would satisfactorily explain the paroxysmal rises in blood pressure. The effects of the excessive

rises in blood pressure in these otherwise normal patients are of interest. Violent headaches may accompany the attacks, and acute pulmonary edema has in several instances been the cause of death.

THE MORTALITY RATE IN UKRANIA

THE GENERAL interest as to the progress of the great social experiment in Russia and the difficulty of obtaining any exact measure of its degree of success or failure make it seem worth while to draw attention to some rather striking figures recently published,[1] which deal with the evolution of the mortality rate in Ukrania.

The author of this analysis of the Ukranian mortality rate, M. Ptoukha, a member of the Academy of Science of that country, states that prior to the middle of the decennium 1890–1900 no significant fall in the mortality rate can be detected. From 1895 until 1914 the mortality rate showed a relatively steady decrease and in the period 1911–1914 it was only 71.6 per cent of its height during the period 1891–1895. An analysis of this period of improvement indicates, however, that a coincident decrease in the birth rate in part is accountable for the figures. In the age period 0–14 a definite lowering of the death rate was detectable, but in the adult age groups little change was observable, and the mortality rate among those over 54 years was actually increasing.

During the World War and the period of ensuing civil war lasting until 1921, the figures available indicate that such improvement in the mortality rate as had occurred between 1895 and 1914 was lost, so that at the beginning of the period of reconstruction the mortality rate was again at least as high as in 1896–1897, the years of a complete census. The author therefore feels that in utilizing the census of 1896–1897 for comparison with that taken in 1926–1927 he is in effect comparing the mortality rates of Ukrania before the Soviet regime and after it had exerted its influence for five years. There is a certain ingenuousness to this hypothesis; the results, however, are none the less interesting.

In comparing the two above periods, the author finds that for the stationary population there was a fall of mortality rate of 21 per cent for males and 24.5 per cent for females. The improvement was most marked in the cities where the rate fell 36.6 per cent for males and 36.1 per cent for females. The life expectancy in the country at large for a new-born male was increased by 10 years and for a new-born female by 12 years.

The reduction in infant mortality (0–1 year) was marked. The mortality rate for male infants in the country at large fell 33.2 per cent and for female infants 34.1 per cent. This improvement was greatest in the industrial centers rather than in the country. For male infants in the four large cities the fall in death rate was 57 per cent and for female infants 58.2 per cent.

[1] PTOUKHA, M.: Evolution de la mortalité en Ukraine avant l'époque du premier plan quinquennal, Jr. du Cycle Med., Kyiv, 1932, ii, 754–757.

Among children of 1–9 years prior to the Soviet regime the mortality rate due to epidemic intestinal disease was always high. A comparison of the two periods chosen shows that there has occurred a fall in the mortality rate of 40 per cent in this age group. In the adult age group, 20–59 years, the interesting observation was made that whereas the mortality rate for men fell 18.8 per cent, that for women fell 38.4 per cent. In earlier periods in Ukrania the death rate for women in this age group had been 8.15 per cent higher than that for men, whereas in 1926–1927 it was found to be 19 per cent lower than the male mortality rate.

The author states that these improvements in the mortality rates are greater than those that have occurred in analogous periods in France, Italy, England, Japan or the United States. He attributes the improvement to the active interest of the Soviet regime in public health measures, particularly in control measures against epidemics, and in the establishment of institutions for the protection of maternity cases and for the care of infants and children.

The record as stated seems to afford Ukrania just cause for pride. From such uncertain reports as have come from that large walled-off section of our world, there has been reason to doubt whether the social experiment in progress there was conducive to either the health or happiness of the citizens. Here, at least, is some tangible evidence that in the first respect definite advances are being made.

In the last paragraph of the author's article he quotes Stalin who, in addressing the Central Committee of the Sixteenth Assembly of the Communist Party, attributed the achievement of the lowered mortality rate to the repartition of the national revenue which had given to the laboring classes the opportunity of improving the sanitary and hygienic conditions of their lives. In 1929–1930, stated Stalin, 98 per cent of the national income went to the industrial workers and peasants and only 2 per cent to the class of exploiters. Those who believe that only a government which acts in a spirit of justice to all and favor to none is likely to bring about the happiness of its people may, after the above statement, still retain some doubts as to the ultimate success in this respect of the Soviet Republics. We should like at least to know how large a percentage of the population was included in the class which received only 2 per cent of the national income and what the mortality rate was in this class in the period under discussion.

REVIEWS

Nervous Breakdown. By W. Beran Wolfe, M.D., Director of the Community Church Mental Hygiene Clinic, New York City. 240 pages. Farrar and Rinehart, New York. Price, $2.50.

This very attractively written "handbook" will undoubtedly receive both commendation and criticism and it will be widely read because it treats of a subject ever present in society. Unfortunately, the author's discussion of human behavior would lead a lay reader to the belief that the straightening out of a "nervous breakdown" is a very simple matter. Although the author attempts to disarm criticism by making some sweeping statements about quackery, he himself seems to place psychiatry on a pedestal and to imply that psychiatrists have an open sesame. He says in his preface: "If you cannot find any evidence of physical or organic disease, consult a psychiatrist." The author also says on page 184: "I wish we could talk it over face to face." And on the next page: "If you like, you can sit down and write me your life story and thus hold a community conversation with me. You can always do that if you are lonely." Since the neurotic individual is continually looking for a sympathetic ear there will no doubt be a bountiful response to his advice.

The author has presented in this volume some very graphic cases and expresses on the whole a very sound viewpoint. Very few psychiatrists will take an exception to his explanations of mechanisms as he does not align himself with any specific school of psychology. His discussions in the last two chapters are the weakest part of his book, but the first five chapters will keep the readers interested without difficulty. This handbook will at least stimulate the reader, whether professional or lay, to a more extensive reading of the subject of why people behave the way they do.

J. L. McC.

Urine and Urinalysis. By Louis Gershenfeld, Ph.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. 272 pages, illustrated with 36 engravings. Lea and Febiger, Philadelphia. 1933. Price, $2.75.

This book has been written, according to the author, to meet the needs and the requisites of graduates in pharmacology, chemistry, bacteriology, the nursing profession, technicians, and many practitioners in medicine "interested solely in the performance of urinalyses" and hence anxious to have an up-to-date monograph on this subject.

Following a brief historical consideration of urinalysis and a very cursory description of the internal structure and function of the kidneys, various chapters are devoted to the physical and chemical composition of the urine, qualitative tests of various sorts, quantitative estimations, the microscopic examination of urine, and special tests under which are included the analysis of urinary calculi, tests for inorganic metallic poisons, bacteriologic investigations, and tests of various sorts for renal function.

The content of the book is well though tersely presented. The tests advised are, for the most part, the standard ones which have been in existence for many years, both qualitative and quantitative in character. No gross inaccuracies were discovered. Not much space is devoted to the interpretation of the various tests, and the many possible sources of error, though one would scarcely expect the inclusion of such matter, in view of the fact that apparently the book has been written for the technician who performs the tests, but who is not required to interpret the clinical value

of the results. The book can be recommended as fulfilling precisely those purposes for which it was written.

S. R. M.

A New Approach to Dietetic Therapy. By EUGENE FÖLDES, M.D., Formerly Assistant Professor of Medicine, University of Budapest, Hungary. xii + 434 pages. Richard G. Badger, Boston, 1933. Price, $5.00.

The author believes that a disordered water and mineral metabolism is responsible, in whole or in part, for many disease conditions. The first part of the book is given over to a discussion of the physiology and general pathology of water and mineral metabolism, the work of the author himself being particularly stressed. His dietetic therapy is directed particularly to the elimination of retained mineral substances. The book contains various novel suggestions. The bibliography is extensive and refers very largely to the German literature. In the opinion of the reviewer the book is a medley of half-baked theorizing, based upon very dubious physiological grounds. Whether the therapeutic claims which the author makes may be justified upon empirical grounds, is, of course, another matter, but to this reader they are not convincing.

G. A. H.

Dietetics for the Clinician. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P.; in collaboration with RUTH LOTHROP GALLUP, dietitian; foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University. 666 pages. Lea and Febiger, Philadelphia. 1933. Price, $6.50.

In spite of the many books on dietetics which are already available, the reviewer feels that Dr. Bridges has justified himself in adding another volume to this literature. In the first place, the book is written with a freshness and candor which are very attractive. The author shows that he is aware not only of the importance of his subject but also of the deficiencies in our knowledge concerning it. The value of diet when definitely known is stressed but no attempt is made to raise dietetic therapy to the level of a panacea. Many data not usually found in similar textbooks are included in this volume and in readily accessible form. The classified tables cover practically all of the chemical constituents.

The dietetic treatment of the separate diseases is presented by a group of contributors. This section of the book is a valuable one. There is of necessity some repetition since each section is self-contained.

In what is said of the treatment of duodenal ulcer it seems that there is over emphasis on meticulous dietary measures. Ambulatory treatment is mentioned, but for the patient to live up to the exacting regulations prescribed it would almost always be necessary that he be hospitalized. For the important disease, ulcerative colitis, no treatment is mentioned, though considerable space is devoted to proctitis, pruritis ani, and spastic colitis.

L. M.

Diseases of the Mouth. By STERLING V. MEAD, D.D.S., M.S., B.S., Professor of Oral Surgery and Diseases of the Mouth, and Director of Research, Georgetown University Dental School; Professor of Diseases of the Mouth, Georgetown University Medical School. 932 pages; 18 x 25 cm. C. V. Mosby Co., St. Louis. 1932. Price, $10.00.

The author has attempted in this volume to meet the needs of students of both medicine and dentistry for knowledge of the various disease processes affecting the

structures of the mouth. Roughly the first third of the book is given up to a consideration of conditions affecting the teeth and the remaining two-thirds to diseases of the soft tissues, lips, tongue, throat, salivary glands, and of the bones, articulations and the maxillary sinuses. The subjects of stomatitis and of tumors of the mouth region are taken up in separate chapters.

The medical aspects of these diseases are discussed in an elementary way which will not be of value to the average medical reader. Space devoted to such topics as the methods of taking the temperature, counting the blood cells, and using the routine bacteriologic smears is waste space as far as he is concerned. On the other hand the average medical student will profit by the discussion of diseases and abnormalities of the teeth.

To the reviewer, the chapters on the diseases of the lips, tongue, throat, etc. are disappointing. The descriptions of the appearance and characteristics of the various lesions are too vague to be of assistance. The clinical course of these lesions is dealt with only in the briefest and most inadequate manner. The illustrations to these sections are, however, often excellent. The relation of the section on diseases of the blood to the subject of the book is not made as apparent as it should be. For example, in discussing leukemia the author does not even mention the dangers of dental extractions in this condition.

On the whole, the book is of little value to the student of medicine.

M. C. P.

Some Factors in the Localization of Disease in the Body. By HAROLD BURROWS. 299 pages. William Wood and Company, Baltimore, 1932. Price, $4.50.

The author discusses in this interesting monograph the present status of our knowledge concerning those factors which determine the localization in certain tissues of morbific matter carried in the blood stream. In the first part of the book he has collected under separate chapter heads what is known concerning the localization of normal and foreign proteins, of dyes and fine inorganic particles and natural pigments, of syphilis, of bacteria and viruses, and of cancer. The author has the gift of clarity of expression and he has presented the scientific data in sufficient detail so that the reader may form an independent judgment of its significance.

The nature and causes of increased capillary permeability are dealt with in Part II; the forces at play in the transport of material from the blood stream into the tissues are analyzed; and the tendency of an inflammatory process to fix colloidal and other foreign material is discussed. Many interesting data bearing on the question of local immunity are presented. Finally the author attempts to show the bearing of these principles of localization upon our therapeutic practices.

The author is a stimulating guide through a field of general pathology with which most physicians are unfamiliar. His book will re-awaken in many an interest in the fundamental mechanisms of disease.

M. C. P.

Anleitung zur frühzeitigen Erkennung der Krebskrankheit. 134 pages. S. Hirzel, Leipzig, 1932. Price, Reichmark 3.

This small manual was first issued in 1917 as a part of the campaign against cancer in Saxony. The present second edition has been revised by a committee including prominent names from the University clinics in Dresden and Leipzig. The book has been written for the general practitioner upon whom the success of any campaign for the early recognition of cancer depends. It should be of great assistance to him. The introductory matter is brief, consisting of short sections on cancer mortality, the general nature of cancer, diagnostic local and general signs, indications

and contraindications for operation, practical rules governing biopsy, etc. The general characteristics of cancer behavior in the chief tissue of the body, skin, mucous membrane, glands, bone, etc., are then summarized. The major portion of the book is given up to a discussion of the early cancerous lesions of each region of the body, beginning with the scalp and covering both the exterior and interior of the body.

Few small books contain as much valuable information so clearly and concisely expressed. The commoner precancerous and cancerous lesions of each region are described as to appearance and early symptoms, diagnostic findings, clinical course, and therapeutic indications. The sections read like the best type of clinical lectures, thorough, clearly organized, forceful and eminently practical.

This manual deserves careful reading by all those interested in similar campaigns in this country. It seems a model of its kind.

M. C. P.

COLLEGE NEWS NOTES

Among gifts to the College Library of publications by members herewith acknowledged are the following:

Dr. Priscilla White (Fellow), Boston, Mass.—1 book, "Diabetes in Childhood and Adolescence";

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;

Dr. Louis I. Kramer (Associate), Providence, R. I.—2 reprints;

Dr. Marjorie E. Reed (Associate), Plymouth, Pa.—2 reprints;

Dr. Karl Rothschild (Fellow), New Brunswick, N. J.—2 reprints;

Dr. Walter M. Simpson (Fellow), Dayton, Ohio—4 reprints.

Dr. Edwin W. Gehring, Fellow and Governor of the College for Maine, has been named President-elect of the Maine Medical Association for the coming year.

Dr. Francis B. Johnson (Fellow), Professor of Clinical Pathology of the Medical College of the State of South Carolina, Charleston, was recently elected President of the Tri-State Medical Association of the Carolinas and Virginia.

Dr. George C. Bower (Associate) has left the State Hospital at Willard, N. Y., to accept a promotion as first-grade pathologist at the State Hospital at Marcy, N. Y.

Major E. C. Odom (Fellow) has completed four years of duty at the Walter Reed General Hospital, Washington, D. C., and has now been transferred to the Letterman General Hospital, San Francisco.

Dr. Gerald B. Webb (Fellow), Colorado Springs, was elected President of the Colorado State Board of Medical Examiners on July 11.

Dr. Janvier W. Lindsay (Fellow) and Admiral Cary T. Grayson (Associate) have been put in charge of the Pathologic Laboratory and the Warwick Clinic, respectively, of the Garfield Memorial Hospital. The radiologic department of this Hospital has been enlarged through the establishment of the Warwick Clinic, a bequest of the late Randolph T. Warwick. The bequest provided for the establishment of an institute "for the care and treatment of women afflicted with cancer."

Dr. George R. Minot (Fellow), Professor of Medicine of the Harvard University Medical School, Boston, was recently awarded the Moxon gold medal of the Royal College of Physicians of England.

Dr. Lewis J. Moorman (Fellow), Oklahoma City, succeeded to the Superintendency of the State University Hospitals, Oklahoma City.

Dr. G. Bruce Lemmon (Fellow) has been appointed Consultant in Internal Medicine at the Federal Hospital for Defective Delinquents. This hospital, which has just been completed at Springfield, Missouri, has 705 beds and cost over $2,000,000. Dr. Lawrence Kolb (Fellow) of the U. S. Public Health Service is its superintendent. The institution will be known as the Medical Center for the Department of Justice, and is the first of its kind.

OBITUARIES

DR. EDWARD OSGOOD OTIS

On May 28, 1933, Dr. Edward Osgood Otis died in his eighty-fifth year. At the time of his death Dr. Otis was a Governor for the American College of Physicians for New Hampshire. He had previously been a Governor for the College for Massachusetts but he had retired from active practice and had gone to live at Exeter, New Hampshire. Dr. Otis had been a Fellow of the American College of Physicians since 1920 and was the oldest member in respect to age of the College. Throughout his membership Dr. Otis had taken a very active interest in the College. He was one of those long, lean Yankees who never look their age and who are active physically and mentally until the end. It was with great regret that Dr. Otis was obliged to forego attendance at the meeting of the College in Montreal. Although he maintained his residence for the last few years in Exeter, New Hampshire, he came frequently to Boston to attend meetings and to lend his presence to important occasions.

Dr. Otis was born in 1848 at Rye, New Hampshire, went to Phillips Exeter Academy, received his bachelor degree at Harvard in 1871 and his medical degree also at Harvard in 1877. After an internship at the Boston City Hospital he took postgraduate work in Vienna. On his return he established an office in Boston and devoted himself from the beginning to diseases of the chest. In those days that meant largely tuberculosis. For 45 years Dr. Otis was associated with the Boston Dispensary and in his chest clinic there he gave instruction to the medical students. For many years he was professor of pulmonary diseases and climatology at Tufts College Medical School. Tufts College gave him the honorary degree of Doctor of Sciences which the University of his native state of New Hampshire also conferred upon him.

Dr. Otis acquired a very distinguished position in the practice of medicine in the city of Boston, particularly, of course, in regard to tuberculosis and other chronic diseases of the chest. He was instrumental in all activities in regard to tuberculosis. For years he was a visiting and consultant physician for the Massachusetts State Sanatorium at Rutland which was the first state institution for the early care of tuberculosis. He was a director of the National Tuberculosis Association. He had been president of the Massachusetts Tuberculosis League and President of the Boston Tuberculosis Association. He was an early member and ex-president of the American Climatological and Clinical Association and he contributed many articles and papers to the current medical journals. He was the author of " Pulmonary Tuberculosis " and " Tuberculosis—Its Cause, Cure and Prevention." Dr. Otis had watched the development of internal medicine and of his specialty, tuberculosis, from its very beginnings as a science to its present state. In that rapid progress of internal medicine and of knowledge concerning tuberculosis which left so many of his generation

behind he was always in the forefront, one of the leaders. His was a shrewd and cautious nature which did not run to fads but which could become enthusiastic over developments while they were still new. The Yankee twang in his speech was a guarantee of his horse sense, and his apparently stern exterior covered great warmth of affection and intense personal loyalty.

ROGER I. LEE, M.D., F.A.C.P.,
Governor of the College
for Massachusetts

DR. RAYMOND JOSEPH HARRIS

Dr. Raymond Joseph Harris was born in Philadelphia in 1872 and educated in the public schools there, graduating from the Central High School with the degrees of A.B. and A.M. He matriculated in the Hahnemann Medical College of Philadelphia, graduating in 1894. From 1895 to 1902 Dr. Harris served as Demonstrator of Chemistry at his Alma Mater. For a number of years he was Associate Physician at the Broad Street Hospital, Philadelphia.

Dr. Harris died suddenly August 9, 1933, as a result of a coronary thrombosis.

E. J. G. BEARDSLEY, M.D., F.A.C.P.,
Governor of the College
for (Eastern) Pennsylvania

DR. SHANNON LAURIE VAN VALZAH

Born September 18, 1888; B.A., University of Oregon, 1910; M.D., Johns Hopkins University Medical School, 1914; Postgraduate work in Tropical Medicine, Bacteriology, Hygiene and Military Science, Army Medical School, October 1916, to March 1917; entered the Medical Corps as First Lieutenant in 1917 and was promoted to Major in 1918; Assistant and Laboratory Officer, Fitzsimons General Hospital, 1922–24; Assistant Chief of Medical Service, Fitzsimons General Hospital 1926–33; member, Johns Hopkins Medical and Surgical Society and Association of Military Surgeons; Fellow, American Medical Association and American College of Physicians; died July 9, 1933, of diverticulitis of the sigmoid and peritonitis.

Major Van Valzah entered the Medical Corps of the U. S. Army in 1917 during the World War, did service in France with great credit to the Medical Corps and himself. After his return to the United States, while on duty at an eastern station, he developed pulmonary tuberculosis, and in 1922 was sent as a patient to Fitzsimons General Hospital, where he remained as a patient until 1923, when he was assigned to duty at that hospital. His outstanding ability soon became manifest and he was detailed as Assistant to the Chief of the Medical Service and in charge of electrocardio-

graphy. This position he filled with great credit until his death, at Fitzsimons General Hospital, Denver, Colorado.

Major Van Valzah, had, for some years, come to consider Denver his home and planned to live there on retirement from active service from the Army. He was one of those lovable individuals whose conduct was marked by kindness and consideration for others. His conferees loved him for himself, respected and admired him for his professional ability and knowledge. His friends both professional and lay were legion.

He was married in 1916 to Miss Ola Summers of Baltimore who survives him—a charming and devoted wife who has lost a kind and loving husband. The Army has lost a beloved Physician and Officer.

A. C. Cooper, M.D., F.A.C.P.,
Lt. Col., Medical Corps,
U. S. Army.